

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>7</sup> : C07D 487/04, A61K 31/519, A61P 25/00		A2	(11) International Publication Number: <b>WO 00/59908</b>
			(43) International Publication Date: 12 October 2000 (12.10.00)
(21) International Application Number: PCT/US00/09111 (22) International Filing Date: 6 April 2000 (06.04.00) (30) Priority Data: 60/128,006 6 April 1999 (06.04.99) US (71) Applicant: DU PONT PHARMACEUTICALS COMPANY [US/US]; Chestnut Run Plaza, 974 Centre Road, Wilming- ton, DE 19807 (US). (72) Inventors: GILLIGAN, Paul, J.; 2629 Pennington Drive, Wilmington, DE 19810 (US). WILDE, Richard, G.; 205 Roseman Court, Newark, DE 19711 (US). (74) Agent: RUBIN, Kenneth, B.; Du Pont Pharmaceuticals Com- pany, Legal Patent Records Center, 1007 Market Street, Wilmington, DE 19898 (US).		(81) Designated States: AU, BR, CA, CN, CZ, EE, HU, IL, IN, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SG, SI, SK, TR, UA, VN, ZA, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>Without international search report and to be republished          upon receipt of that report.</i>	
(54) Title: PYRAZOLOPYRIMIDINES AS CRF ANTAGONISTS			
<div style="text-align: center;"> <p>( I )</p> </div>			
(57) Abstract  The present invention relates to pyrazolopyrimidines according to formula (I) and stereoisomers, isomers and salts thereof wherein R <sup>1</sup> -R <sup>5</sup> are selected from certain alkyl, aryl and heteroaryl species as defined in the specification wherein all of the compounds are useful as CRF antagonists and are thus useful in the treatment of neurological disorders as well as a multitude of other CRF associated diseases or conditions.			

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

TITLE

## PYRAZOLOPYRIMIDINES AS CRF ANTAGONISTS

5

FIELD OF THE INVENTION

The present invention relates to novel compounds, compositions, and methods for the treatment of psychiatric disorders and neurological diseases, including major depression, anxiety-related disorders, post-traumatic stress disorder, supranuclear palsy and feeding disorders, as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress. In particular, the present invention relates to novel pyrazolo[1,5-a]pyrimidines, pharmaceutical compositions containing such compounds and their use in treating psychiatric disorders, neurological diseases, immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress.

BACKGROUND OF THE INVENTION

Corticotropin releasing factor (herein referred to as CRF), a 41 amino acid peptide, is the primary physiological regulator of proopiomelanocortin (POMC) - derived peptide secretion from the anterior pituitary gland [J. Rivier et al., Proc. Nat. Acad. Sci. (USA) 80:4851 (1983); W. Vale et al., Science 213:1394 (1981)]. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in brain [W. Vale et al., Rec. Prog. Horm. Res. 39:245 (1983); G.F. Koob, Persp. Behav. Med. 2:39 (1985); E.B. De

Souza et al., J. Neurosci. 5:3189 (1985)]. There is also evidence that CRF plays a significant role in integrating the response of the immune system to physiological, psychological, and immunological stressors [J.E. Blalock, Physiological Reviews 69:1 (1989); J.E. Morley, Life Sci. 41:527 (1987)].

Clinical data provide evidence that CRF has a role in psychiatric disorders and neurological diseases including depression, anxiety-related disorders and feeding disorders. A role for CRF has also been postulated in the etiology and pathophysiology of Alzheimer's disease, Parkinson's disease, Huntington's disease, progressive supranuclear palsy and amyotrophic lateral sclerosis as they relate to the dysfunction of CRF neurons in the central nervous system [for review see E.B. De Souza, Hosp. Practice 23:59 (1988)].

In affective disorder, or major depression, the concentration of CRF is significantly increased in the cerebral spinal fluid (CSF) of drug-free individuals [C.B. Nemeroff et al., Science 226:1342 (1984); C.M. Banki et al., Am. J. Psychiatry 144:873 (1987); R.D. France et al., Biol. Psychiatry 28:86 (1988); M. Arato et al., Biol Psychiatry 25:355 (1989)]. Furthermore, the density of CRF receptors is significantly decreased in the frontal cortex of suicide victims, consistent with a hypersecretion of CRF [C.B. Nemeroff et al., Arch. Gen. Psychiatry 45:577 (1988)]. In addition, there is a blunted adrenocorticotropin (ACTH) response to CRF (i.v. administered) observed in depressed patients [P.W. Gold et al., Am J. Psychiatry 141:619 (1984); F. Holsboer et al., Psychoneuroendocrinology 9:147 (1984); P.W. Gold et al., New Eng. J. Med. 314:1129 (1986)]. Preclinical studies in rats and non-human primates provide additional support for the hypothesis that hypersecretion of CRF may be involved in the symptoms seen in human depression [R.M. Sapolsky, Arch. Gen. Psychiatry 46:1047 (1989)]. There is preliminary evidence that tricyclic antidepressants

can alter CRF levels and thus modulate the numbers of CRF receptors in brain [Grigoriadis et al., Neuropsychopharmacology 2:53 (1989)].

It has also been postulated that CRF has a role in the etiology of anxiety-related disorders. CRF produces anxiogenic effects in animals and interactions between benzodiazepine / non-benzodiazepine anxiolytics and CRF have been demonstrated in a variety of behavioral anxiety models [D.R. Britton et al., Life Sci. 31:363 (1982); C.W. Berridge and A.J. Dunn Regul. Peptides 16:83 (1986)]. Preliminary studies using the putative CRF receptor antagonist  $\alpha$ -helical ovine CRF (9-41) in a variety of behavioral paradigms demonstrate that the antagonist produces "anxiolytic-like" effects that are qualitatively similar to the benzodiazepines [C.W. Berridge and A.J. Dunn Horm. Behav. 21:393 (1987), Brain Research Reviews 15:71 (1990)].

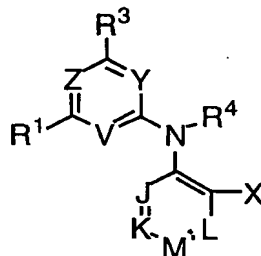
Neurochemical, endocrine and receptor binding studies have all demonstrated interactions between CRF and benzodiazepine anxiolytics, providing further evidence for the involvement of CRF in these disorders. Chlordiazepoxide attenuates the "anxiogenic" effects of CRF in both the conflict test [K.T. Britton et al., Psychopharmacology 86:170 (1985); K.T. Britton et al., Psychopharmacology 94:306 (1988)] and in the acoustic startle test [N.R. Swerdlow et al., Psychopharmacology 88:147 (1986)] in rats. The benzodiazepine receptor antagonist (Ro15-1788), which was without behavioral activity alone in the operant conflict test, reversed the effects of CRF in a dose-dependent manner while the benzodiazepine inverse agonist (FG7142) enhanced the actions of CRF [K.T. Britton et al., Psychopharmacology 94:306 (1988)].

It has been further postulated that CRF has a role in immunological, cardiovascular or heart-related diseases such as hypertension, tachycardia and congestive heart failure, stroke, osteoporosis, premature birth, psychosocial dwarfism, stress-induced

fever, ulcer, diarrhea, post-operative ileus and colonic hypersensitivity associated with psychopathological disturbance and stress.

The mechanisms and sites of action through which the standard anxiolytics and antidepressants produce their therapeutic effects remain to be elucidated. It has been hypothesized however, that they are involved in the suppression of the CRF hypersecretion that is observed in these disorders. Of particular interest is that preliminary studies examining the effects of a CRF receptor antagonist ( $\alpha$ -helical CRF9-41) in a variety of behavioral paradigms have demonstrated that the CRF antagonist produces "anxiolytic-like" effects qualitatively similar to the benzodiazepines [for review see G.F. Koob and K.T. Britton, In: Corticotropin-Releasing Factor: Basic and Clinical Studies of a Neuropeptide, E.B. De Souza and C.B. Nemeroff eds., CRC Press p221 (1990)].

DuPont Merck PCT application US94/11050 describes corticotropin releasing factor antagonist compounds of the formula:

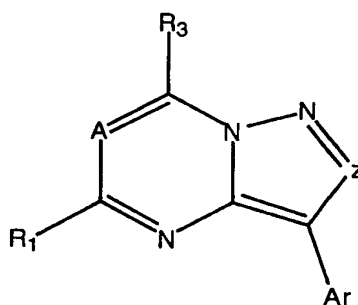


and their use to treat psychiatric disorders and neurological diseases. Included in the description are fused pyridines and pyrimidines of the formula:

5

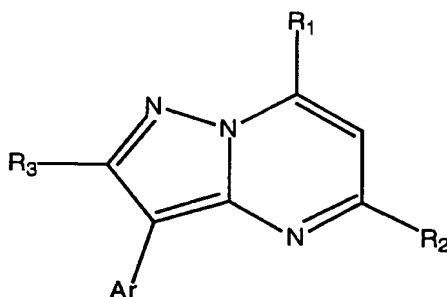
where: V is CR<sup>1a</sup> or N; Z is CR<sup>2</sup> or N; A is CR<sup>30</sup> or N; and D is CR<sup>28</sup> or N.

WO 98/03510, published in January, 1998, also describes a series of CRF antagonist compounds having the  
5 formula:



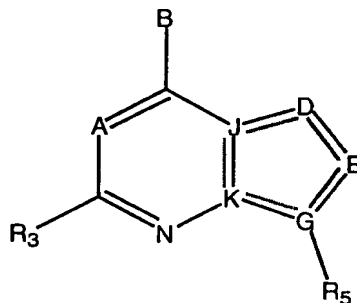
wherein z is N or CR<sup>2</sup> and A is N or CR.

WO 97/29109, published in August, 1997, similarly  
10 describes certain CRF antagonist compounds having the formula:



wherein Ar is phenyl, pyridyl and substituted versions  
15 thereof.

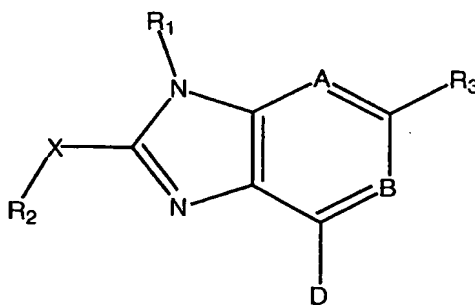
WO 98/08847, published March 5, 1998, discloses CRF antagonist compounds of the formula:



6

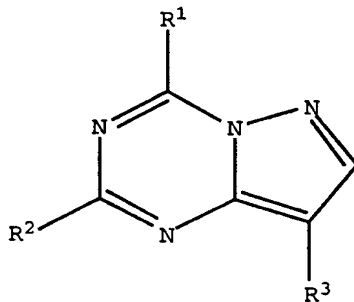
wherein B is selected from a variety of non-aryl groups and R<sup>5</sup> is selected from certain groups such as phenyl or pyridyl or substituted versions thereof.

WO 99/01454, published on January 14, 1999,  
5 discloses CRF antagonist compounds of the formula:



wherein D is an aryl or heteroaryl group and R<sup>1</sup> is selected from certain non-aryl or non-heteroaryl groups.

10 EP 0 269 859 (Ostuka, 1988) discloses pyrazolotriazine compounds of the formula



15 where R<sup>1</sup> is OH or alkanoyl, R<sup>2</sup> is H, OH, or SH, and R<sup>3</sup> is an unsaturated heterocyclic group, naphthyl or substituted phenyl, and states that the compounds have xanthine oxidase inhibitory activity and are useful for treatment of gout.

20 EP 0 594 149 (Ostuka, 1994) discloses pyrazolotriazine and pyrazolopyrimidine compounds of the formula

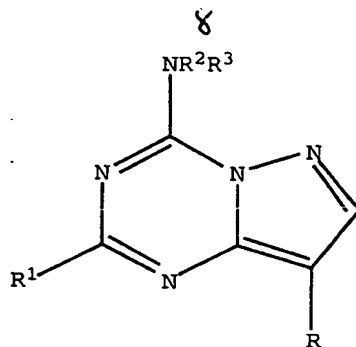


where A is CH or N, R<sup>0</sup> and R<sup>3</sup> are H or alkyl, and R<sup>1</sup> and R<sup>2</sup> are H, alkyl, alkoxyl, alkylthio, nitro, etc., and  
5 states that the compounds inhibit androgen and are useful in treatment of benign prostatic hypertrophy and prostatic carcinoma.

US 3,910,907 (ICI, 1975) discloses pyrazolotriazines of the formula:  
10

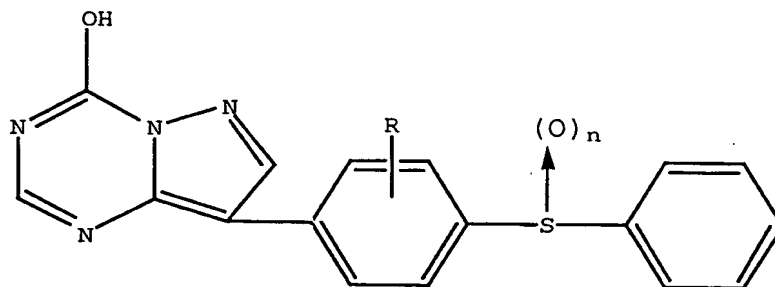
where R<sup>1</sup> is CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub> or C<sub>6</sub>H<sub>5</sub>, X is H, C<sub>6</sub>H<sub>5</sub>, m-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, CN, COOEt, Cl, I or Br, Y is H, C<sub>6</sub>H<sub>5</sub>, o-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, or p-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>,  
15 and Z is OH, H, CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, C<sub>6</sub>H<sub>5</sub>, n-C<sub>3</sub>H<sub>7</sub>, i-C<sub>3</sub>H<sub>7</sub>, SH, SCH<sub>3</sub>, NHC<sub>4</sub>H<sub>9</sub>, or N(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>, and states that the compounds are c-AMP phosphodiesterase inhibitors useful as bronchodilators.

US 3,995,039 discloses pyrazolotriazines of the  
20 formula:



where R<sup>1</sup> is H or alkyl, R<sup>2</sup> is H or alkyl, R<sup>3</sup> is H, alkyl, alkanoyl, carbamoyl, or lower alkylcarbamoyl, and R is  
 5 pyridyl, pyrimidinyl, or pyrazinyl, and states that the compounds are useful as bronchodilators.

US 5,137,887 discloses pyrazolotriazines of the formula



10

where R is lower alkoxy, and teaches that the compounds are xanthine oxidase inhibitors and are useful for treatment of gout.

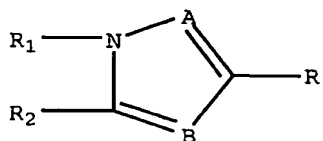
15 US 4,892,576 discloses pyrazolotriazines of the formula

20 where X is O or S, Ar is a phenyl, naphthyl, pyridyl or thienyl group, R<sub>6</sub>-R<sub>8</sub> are H, alkyl, etc., and R<sub>9</sub> is H,

9

alkyl, phenyl, etc. The patent states that the compounds are useful as herbicides and plant growth regulants.

US 5,484,760 and WO 92/10098 discloses herbicidal compositions containing, among other things, a herbicidal  
5 compound of the formula



where A can be N, B can be CR<sub>3</sub>, R<sub>3</sub> can be phenyl or  
10 substituted phenyl, etc., R is -N(R<sub>4</sub>)SO<sub>2</sub>R<sub>5</sub> or -SO<sub>2</sub>N(R<sub>6</sub>)R<sub>7</sub>  
and R<sub>1</sub> and R<sub>2</sub> can be taken together to form

15 where X, Y and Z are H, alkyl, acyl, etc. and D is O or S.

US 3,910,907 and Senga et al., J. Med. Chem., 1982, 25, 243-249, disclose triazolotriazines cAMP phosphodiesterase inhibitors of the formula

20

where Z is H, OH, CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, C<sub>6</sub>H<sub>5</sub>, n-C<sub>3</sub>H<sub>7</sub>, iso-C<sub>3</sub>H<sub>7</sub>, SH, SCH<sub>3</sub>, NH(n-C<sub>4</sub>H<sub>9</sub>), or N(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>, R is H or CH<sub>3</sub>, and R<sub>1</sub> is CH<sub>3</sub>  
25 or C<sub>2</sub>H<sub>5</sub>. The reference lists eight therapeutic areas where inhibitors of cAMP phosphodiesterase could have utility: asthma, diabetes mellitus, female fertility control, male infertility, psoriasis, thrombosis, anxiety, and hypertension.

WO95/35298 (Otsuka, 1995) discloses pyrazolopyrimidines and states that they are useful as analgesics. The compounds are represented by the formula

5

where Q is carbonyl or sulfonyl, n is 0 or 1, A is a single bond, alkylene or alkenylene, R<sup>1</sup> is H, alkyl, etc., R<sup>2</sup> is naphthyl, cycloalkyl, heteroaryl, substituted phenyl or phenoxy, R<sup>3</sup> is H, alkyl or phenyl, R<sup>4</sup> is H, alkyl, alkoxycarbonyl, phenylalkyl, optionally phenylthio-substituted phenyl, or halogen, R<sup>5</sup> and R<sup>6</sup> are H or alkyl.

EP 0 591 528 (Otsuka, 1991) discloses anti-inflammatory use of pyrazolopyrimidines represented by the formula

20 where R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are H, carboxyl, alkoxycarbonyl, optionally substituted alkyl, cycloalkyl, or phenyl, R<sub>5</sub> is SR<sub>6</sub> or NR<sub>7</sub>R<sub>8</sub>, R<sub>6</sub> is pyridyl or optionally substituted phenyl, and R<sub>7</sub> and R<sub>8</sub> are H or optionally substituted phenyl.

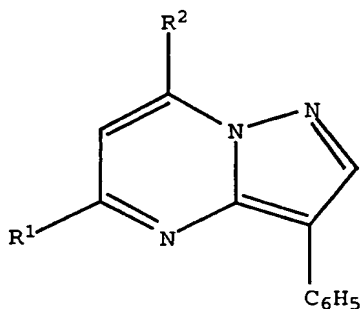
## II

Springer et al, J. Med. Chem., 1976, vol. 19, no. 2, 291-296 and Springer U.S. patents 4,021,556 and 3,920,652 disclose pyrazolopyrimidines of the formula

5

where R can be phenyl, substituted phenyl or pyridyl, and their use to treat gout, based on their ability to inhibit xanthine oxidase.

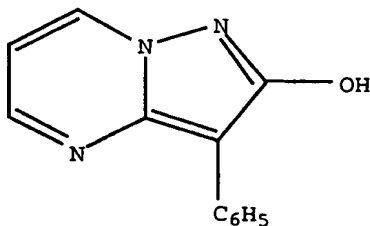
10 Joshi et al., J. Prakt. Chemie, 321, 2, 1979, 341-344, discloses compounds of the formula



15 where R<sup>1</sup> is CF<sub>3</sub>, C<sub>2</sub>F<sub>5</sub>, or C<sub>6</sub>H<sub>4</sub>F, and R<sup>2</sup> is CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, CF<sub>3</sub>, or C<sub>6</sub>H<sub>4</sub>F.

Maquestiau et al., Bull. Soc. Belg., vol.101, no. 2, 1992, pages 131-136 discloses a pyrazolo[1,5-a]pyrimidine of the formula

20



12

Ibrahim et al., Arch. Pharm. (weinheim) 320, 487-491 (1987) discloses pyrazolo[1,5-a]pyrimidines of the formula

5

where R is NH<sub>2</sub> or OH and Ar is 4-phenyl-3-cyano-2-aminopyrid-2-yl.

Other references which disclose azolopyrimidines  
10 included EP 0 511 528 (Otsuka, 1992), US 4,997,940 (Dow, 1991), EP 0 374 448 (Nissan, 1990), US 4,621,556 (ICN,1997), EP 0 531 901 (Fujisawa, 1993), US 4,567,263 (BASF, 1986), EP 0 662 477 (Isagro, 1995), DE 4 243 279 (Bayer, 1994), US 5,397,774 (Upjohn, 1995), EP 0 521 622  
15 (Upjohn, 1993), WO 94/109017 (Upjohn, 1994), J. Med. Chem., 24, 610-613 (1981), and J. Het. Chem., 22, 601 (1985) or others as additionally described herein.

20

#### SUMMARY OF THE INVENTION

In accordance with one aspect, the present invention provides novel compounds which bind to corticotropin releasing factor receptors, thereby  
25 altering the anxiogenic effects of CRF secretion. The compounds of the present invention are useful for the treatment of psychiatric disorders and neurological diseases, anxiety-related disorders, post-traumatic stress disorder, supranuclear palsy and feeding  
30 disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic

13

hypersensitivity associated with psychopathological disturbance and stress in mammals.

According to another aspect, the present invention  
5 provides novel compounds of formula (I) (described  
below) which are useful as antagonists of the  
corticotropin releasing factor. The compounds of the  
present invention exhibit activity as corticotropin  
10 releasing factor antagonists and appear to suppress CRF  
hypersecretion. The present invention also includes  
pharmaceutical compositions containing such compounds  
of formula (I), and methods of using such compounds for  
the suppression of CRF hypersecretion, and/or for the  
treatment of anxiogenic disorders.

15

According to yet another aspect, the present  
invention provides novel compounds, pharmaceutical  
compositions and methods which may be used in the  
treatment of affective disorder, anxiety, depression,  
20 irritable bowel syndrome, post-traumatic stress  
disorder, supranuclear palsy, immune suppression,  
Alzheimer's disease, gastrointestinal disease, anorexia  
nervosa or other feeding disorder, drug or alcohol  
withdrawal symptoms, drug addiction, inflammatory  
25 disorder, fertility problems, disorders, the treatment  
of which can be effected or facilitated by antagonizing  
CRF, including but not limited to disorders induced or  
facilitated by CRF, or a disorder selected from  
inflammatory disorders such as rheumatoid arthritis and  
30 osteoarthritis, pain, asthma, psoriasis and allergies;  
generalized anxiety disorder; panic, phobias,  
obsessive-compulsive disorder; post-traumatic stress  
disorder; sleep disorders induced by stress; pain  
perception such as fibromyalgia; mood disorders such as  
35 depression, including major depression, single episode  
depression, recurrent depression, child abuse induced  
depression, and postpartum depression; dysthemia;  
bipolar disorders; cyclothymia; fatigue syndrome;

stress-induced headache; cancer, human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases such as  
5 ulcers, irritable bowel syndrome, Crohn's disease, spastic colon, diarrhea, and post operative ilius and colonic hypersensitivity associated by psychopathological disturbances or stress; eating disorders such as anorexia and bulimia nervosa;  
10 hemorrhagic stress; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone (ADH); obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage (e.g., cerebral ischemia such as cerebral  
15 hippocampal ischemia); excitotoxic neuronal damage; epilepsy; cardiovascular and hear related disorders including hypertension, tachycardia and congestive heart failure; stroke; immune dysfunctions including stress induced immune dysfunctions (e.g., stress  
20 induced fevers, porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, and dysfunctions induced by confinement in chickens, sheering stress in sheep or human-animal interaction related stress in dogs); muscular spasms; urinary  
25 incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; chemical dependencies and addictions (e.g., dependencies on alcohol, cocaine, heroin, benzodiazepines, or other drugs); drug and alcohol  
30 withdrawal symptoms; osteoporosis; psychosocial dwarfism and hypoglycemia in mammals. The preferred uses include treatment of depression and anxiety.

The present invention also relates to the use of a compound of formula I and other compounds generically  
35 and specifically disclosed herein in therapy.

According to a still further aspect of the invention, the compounds provided by this invention (and especially labelled compounds of this invention)



15

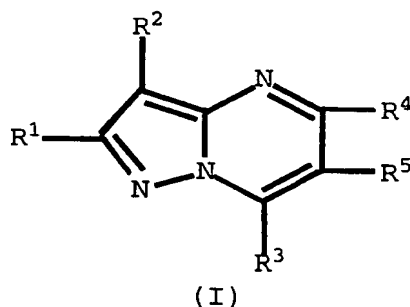
are also useful as standards and reagents in determining the ability of a potential pharmaceutical to bind to the CRF receptor.

5

# DETAILED DESCRIPTION OF INVENTION

[1] Thus, in a first embodiment, the present invention provides a novel compound of formula I:

10



or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

15

R<sup>1</sup> is selected from the group consisting of

- C<sub>1-6</sub> alkyl,
- 20 C<sub>2-10</sub> alkenyl,
- C<sub>2-10</sub> alkynyl,
- C<sub>3-6</sub> cycloalkyl,
- C<sub>1-6</sub> alkyloxy,
- C<sub>1-6</sub> alkylS(O)<sub>n</sub>,
- 25 -NR<sup>1a</sup>R<sup>1b</sup> wherein R<sup>1a</sup> and R<sup>1b</sup> are independently selected from
  - H, C<sub>1-4</sub> alkyl, -C(O)C<sub>1-4</sub>alkyl,
  - C(O)NR<sup>1a</sup>R<sup>1b</sup>,
  - O-C(O)C<sub>1-4</sub>alkyl,

16

-XR<sup>1c</sup> wherein R<sup>1c</sup> is selected from H or -C<sub>1-4</sub> alkylaryl;  
X is selected from O or S(O)<sub>n</sub>,

wherein R<sup>1</sup> is substituted with 0-6 substituents selected  
5 from halogen, C<sub>1-4</sub> alkyl, C<sub>1-6</sub> alkyloxy, C<sub>1-4</sub> haloalkyl, -  
NR<sup>1a</sup>R<sup>1b</sup>, -XR<sup>1c</sup>;

R<sup>2</sup> is selected from the group consisting of

- C<sub>1-10</sub> alkyl,
- 10 C<sub>2-10</sub> alkenyl,
- C<sub>2-10</sub> alkynyl,
- C<sub>3-8</sub> cycloalkyl,
- C<sub>3-6</sub> cycloalkyl C<sub>1-6</sub> alkyl,
- C<sub>1-10</sub> alkyloxy,
- 15 C<sub>1-10</sub> alkyloxyC<sub>1-10</sub> alkyl,
- C<sub>1-4</sub> alkoxy C<sub>1-4</sub> alkyl,
- SO<sub>2</sub>-C<sub>1-10</sub>alkyl
- SO<sub>2</sub>R<sup>2a</sup> wherein R<sup>2a</sup> is aryl,
- SO<sub>2</sub>R<sup>2b</sup> wherein R<sup>2b</sup> is heteroaryl,
- 20 -NR<sup>2c</sup>R<sup>2d</sup> wherein R<sup>2c</sup> and R<sup>2d</sup> are independently selected from  
H, C<sub>1-8</sub> alkyl, S(O)<sub>n</sub>C<sub>1-4</sub> alkyl, C(O)NR<sup>2c</sup>R<sup>2d</sup>, CO<sub>2</sub>C<sub>1-4</sub>alkyl,  
C<sub>3-8</sub> cycloalkyl, C<sub>1-6</sub> alkyloxyC<sub>1-6</sub> alkyl, -C(O)C<sub>1-4</sub>alkyl  
or R<sup>2c</sup> and R<sup>2d</sup> may join to form a heterocyclic ring  
having 0-3 heteroatoms selected from O, N or S,
- 25 - halogen,
- CN,
- C(O)L wherein L is selected from NR<sup>2c</sup>R<sup>2d</sup>, C<sub>1-6</sub> alkyl, H,  
-OC<sub>1-6</sub> alkyl, O(CH<sub>2</sub>)<sub>m</sub>OC<sub>1-6</sub>alkyl, O(CH<sub>2</sub>)<sub>m</sub>NR<sup>2c</sup>R<sup>2d</sup>, -OH,
- 30 aryl, heteroaryl or C(O)OC<sub>1-6</sub> alkyl, wherein m is 1-3,  
or more particularly from,  
-C(O)NR<sup>2c</sup>R<sup>2d</sup>,
- C(O)R wherein R is C<sub>1-6</sub> alkyl,

- C(O)OC<sub>1-4</sub> alkyl,
- C(O)O(CH<sub>2</sub>)<sub>2</sub>OR wherein R is C<sub>1-3</sub> alkyl,
- C(O)O(CH<sub>2</sub>)<sub>2</sub>-NHR wherein R is C<sub>1-3</sub> alkyl,
- C(O)O(CH<sub>2</sub>)<sub>2</sub>-NR<sup>2</sup>,
- 5 -C(O)OH,
- C(O)H,
- C(O)Ph,
- C(O)R' wherein R' is aryl, heteroaryl or carboalkoxy;

10

n is 0, 1 or 2;

- R<sup>2</sup> is substituted with 0-3 substituents independently selected from R', R'', R''' wherein R', R'' and R''' are
- 15 independently selected from C<sub>1-6</sub> alkyl, C<sub>3-7</sub> cycloalkyl, hydroxyC<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkyloxyC<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>1-6</sub> alkyloxy, hydroxy, or

- R<sup>2</sup> is substituted with 0-3 substituents independently selected from:
- 20

halogen,

-CN,

-S(O)<sub>n</sub>R<sup>2e</sup> wherein R<sup>2e</sup> is selected from C<sub>1-4</sub> alkyl, C<sub>1-4</sub> haloalkyl, C<sub>1-4</sub> alkyloxy C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl;

25

-COR<sup>2f</sup> wherein R<sup>2f</sup> is selected from H, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> haloalkyl, C<sub>1-4</sub> alkyloxy C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl, and C<sub>3-6</sub> cycloalkylC<sub>1-4</sub> alkyl;

30

-CO<sub>2</sub>R<sup>2g</sup>,

-NR<sup>2g</sup>COR<sup>2f</sup> wherein R<sup>2g</sup> is selected from H, C<sub>1-6</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-6</sub> cycloalkyl C<sub>1-6</sub> alkyl;

-N(COR<sup>2f</sup>)<sub>2</sub>,

18

$-\text{NR}^{2g}\text{CONR}^{2f}\text{R}^{2h}$ , wherein  $\text{R}^{2h}$  is selected from H,  $\text{C}_{1-6}$  alkyl,  $\text{C}_{1-4}$  haloalkyl,  $\text{C}_{1-4}$  alkoxy  $\text{C}_{1-4}$  alkyl,  $\text{C}_{3-6}$  cycloalkyl and  $\text{C}_{3-6}$  cycloalkyl $\text{C}_{1-6}$  alkyl;

5

$-\text{NR}^{2g}\text{CO}_2\text{R}^{2e}$ ,  
 $-\text{CONR}^{2g}\text{R}^{2h}$ ,  
 1-morpholinyl,  
 1-piperidinyl,

10 1-piperazinyl,

and

$\text{C}_{3-8}$  cycloalkyl wherein 0-1 carbon atoms in the  $\text{C}_{4-8}$  cycloalkyl is replaced by a group selected from  $-\text{O}-$ ,  $-\text{S}(\text{O})_n-$ ,  $-\text{NR}^{2g}-$ ,  $-\text{NCO}_2\text{R}^{2e}$ ,  $-\text{NCOR}^{2e}$ ,

15 and  $-\text{NSO}_2\text{R}^{2e}$ ; and wherein  $\text{N}_4$  in

1-piperazinyl is substituted with 0-1 substituents selected from  $\text{R}^{2g}$ ,  $\text{CO}_2\text{R}^{2e}$ ,  $\text{COR}^{2e}$  and  $\text{SO}_2\text{R}^{2e}$ ; or

20 the group  $\text{R}^{2i}$ ,  $\text{R}^{2j}$ ,  $\text{R}^{2k}$ ,  $\text{C}_{1-6}$  alkyl,  $\text{C}_{2-8}$ 

alkenyl,  $\text{C}_{2-8}$  alkynyl, Br, Cl, F, I,  $\text{C}_{1-4}$  haloalkyl,  $-\text{OR}^{2g}$ ,  $-\text{NR}^{2g}\text{R}^{2h}$ ,  $-\text{C}_{1-6}$  alkyl $\text{OR}^{2g}$ , and  $\text{C}_{3-8}$  cycloalkyl which is substituted with 0-1  $\text{R}^{2i}$  and in which 0-1 carbons of  $\text{C}_{4-8}$  cycloalkyl is replaced by  $-\text{O}-$ , wherein

25  $\text{R}^{2i}$  is selected from aryl wherein aryl includes

phenyl, naphthyl, indanyl and indenyl, each

$\text{R}^{2i}$  being substituted with 0-1  $\text{OR}^{2m}$  and 0-5

substituents independently selected from the group  $\text{C}_{1-6}$  alkyl,  $\text{C}_{3-6}$  cycloalkyl, Br, Cl, F, I,  $\text{C}_{1-4}$  haloalkyl,  $-\text{CN}$ ,

30 nitro,  $-\text{SH}$ ,  $-\text{S}(\text{O})_n\text{R}^{2n}$ ,  $-\text{COR}^{2m}$ ,  $-\text{OC}(\text{O})\text{R}^{2n}$ ,  $-\text{NR}^{2g}\text{COR}^{2m}$ ,  $-\text{N}(\text{COR}^{2m})_2$ ,

$-\text{NR}^{2g}\text{CONR}^{2o}\text{R}^{2p}$ ,  $-\text{NR}^{2g}\text{CO}_2\text{R}^{2n}$ ,  $-\text{NR}^{2o}\text{R}^{2p}$  and  $-\text{CONR}^{2o}\text{R}^{2p}$ ;

$R^{2j}$  is selected from heteroaryl wherein heteroaryl includes pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, 2,3-dihydrobenzothienyl-s-oxide, 2,3-dihydro-benzothienyl-S-dioxide, indolinyl, benzoxazolin-2-onyl, benzodioxolanyl and benzodioxane, each heteroaryl being substituted on 0-4 carbon atoms with a substituent independently selected from the group  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl, Br, Cl, F, I,  $C_{1-4}$  haloalkyl, -CN, nitro,  $OR^{2m}$ , -SH,  $-S(O)_nR^{2h}$ ,  $-COR^{2m}$ ,  $-OC(O)R^{2h}$ ,  $-NR^{2g}COR^{2m}$ ,  $-N(COR^{2m})_2$ ,  $-NR^{2g}CONR^{2o}R^{2p}$ ,  $-NR^{2g}CO_2R^{2h}$ ,  $-NR^{2o}R^{2p}$  and  $-CONR^{2o}R^{2p}$  and each heteroaryl being substituted on any nitrogen atom with 0-1 substituents selected from the group  $R^{2g}$ ,  $CO_2R^{2e}$ ,  $COR^{2e}$  and  $SO_2R^{2e}$ ;

$R^{2k}$  is heterocyclyl which is a saturated or partially saturated heteroaryl as defined for  $R^{2j}$ , each heterocyclyl being substituted on 0-4 carbon atoms with a substituent independently selected from the group  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl, Br, Cl, F, I,  $C_{1-4}$  haloalkyl, -CN, nitro,  $-OR^{2m}$ , -SH,  $-S(O)_nR^{2h}$ ,  $-COR^{2m}$ ,  $-OC(O)R^{2h}$ ,  $-NR^{2g}COR^{2m}$ ,  $-N(COR^{2m})_2$ ,  $-NR^{2g}CONR^{2o}R^{2p}$ ,  $NR^{2g}CO_2R^{2h}$ ,  $-NR^{2o}R^{2p}$  and  $-CONR^{2o}R^{2p}$  and each heterocyclyl being substituted on any nitrogen atom with 0-1 substituents selected from the group  $R^{2g}$ ,  $CO_2R^{2e}$ ,  $COR^{2e}$  and  $SO_2R^{2e}$ ;

wherein

$R^{2i}$  is H,  $C_{1-4}$  alkyl,  $C_{3-6}$  cycloalkyl- $C_{1-4}$  alkyl and  $C_{3-8}$  cycloalkyl;

$R^{2m}$  is H,  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl  $C_{1-6}$  alkyl,  $C_{1-2}$  alkyloxy  $C_{1-2}$  alkyl,  $C_{1-4}$  haloalkyl,  $R^{2q}S(O)_n-C_{1-4}$  alkyl and  $R^{2r}R^{2s}N-C_{2-4}$  alkyl;

5

$R^{2n}$  is H,  $C_{1-6}$  alkyl,  $C_{3-10}$  cycloalkyl,  $C_{3-6}$  cycloalkyl- $C_{1-6}$  alkyl,  $C_{1-2}$  alkyloxy  $C_{1-2}$  alkyl, and  $C_{1-4}$  haloalkyl;

$R^{2o}$  and  $R^{2p}$  are independently selected at each occurrence  
10 from H,  $C_{1-6}$  alkyl,  $C_{3-10}$  cycloalkyl,  $C_{3-6}$  cycloalkyl  $C_{1-6}$  alkyl and  $C_{1-4}$  haloalkyl;

$R^{2q}$  is selected from  $C_{1-6}$  alkyl,  $C_{1-4}$  haloalkyl,  $C_{1-4}$  alkoxy- $C_{1-4}$  alkyl,  $C_{3-6}$  cycloalkyl,  $C_{3-6}$  cycloalkyl- $C_{1-6}$  alkyl, aryl,  
15 aryl( $C_{1-4}$  alkyl), heteroaryl and heteroaryl ( $C_{1-4}$  alkyl)- and benzyl, each benzyl being substituted on the aryl moiety with 0-1 substituents selected from the group  $C_{1-4}$  alkyl, Br, Cl, F, I,  $C_{1-4}$  haloalkyl, nitro,  $C_{1-4}$  alkoxy  $C_{1-4}$  haloalkoxy, and dimethylamino;

20

$R^{2r}R^{2s}$  taken together with the N form 1-pyrrolidinyl, 1-morpholinyl, 1-piperidinyl or 1-piperazinyl wherein N<sub>1</sub> in 1-piperiazinyl is substituted with 0-1 substituents selected from the group  $R^{2t}$ ,  $CO_2R^{2q}$ ,  $COR^{2q}$  and  $SO_2R^{2q}$ ;

25

$R^{2t}$  is selected from H,  $C_{1-4}$  alkyl,  $C_{1-4}$  haloalkyl,  $C_{1-4}$  alkoxy- $C_{1-4}$  alkyl,  $C_{3-6}$  cycloalkyl,  $C_{3-6}$  cycloalkyl -  $C_{1-6}$  alkyl, aryl, aryl ( $C_{1-4}$  alkyl)-, heteroaryl and heteroaryl ( $C_{1-4}$  alkyl);

30

$R^3$  is selected from an aryl or heteroaryl group attached through an unsaturated carbon atom;

aryl is selected from phenyl, naphthyl, indanyl and indenyl, each aryl being substituted with 0-5 substituents independently selected at each occurrence from C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, methylenedioxy, C<sub>1-4</sub> alkyloxy-C<sub>1-4</sub> alkyloxy, -OR<sup>2m</sup>, Br, Cl, F, I, C<sub>1-4</sub> haloalkyl, -CN, -NO<sub>2</sub>, -SH, -S(O)<sub>n</sub>R<sup>2n</sup>, -COR<sup>2m</sup>, -CO<sub>2</sub>R<sup>2m</sup>, -OC(O)R<sup>2n</sup>, -NR<sup>2g</sup>COR<sup>2m</sup>, -N(COR<sup>2m</sup>)<sub>2</sub>, -NR<sup>2g</sup>CONR<sup>2o</sup>R<sup>2p</sup>, -NR<sup>2g</sup>CO<sub>2</sub>R<sup>2h</sup>, -NR<sup>2o</sup>R<sup>2p</sup> and CONR<sup>2o</sup>R<sup>2p</sup> and up to 1 phenyl, each phenyl substituent being substituted with 0-4 substituents selected from the group C<sub>1-3</sub> alkyl, C<sub>1-3</sub> alkoxy, Br, Cl, F, I, -CN, dimethylamino, CF<sub>3</sub>, C<sub>2</sub>F<sub>5</sub>, OCF<sub>3</sub>, SO<sub>2</sub>Me and acetyl;

heteroaryl is selected from the group pyridyl, pyrimidyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzo-furanyl, 2,3-dihydrobenzothienyl, 2,3-dihydro-benzothienyl-S-oxide, 2,3-dihydrobenzothienyl-s-dioxide, indolinyl, benzoxazolin-2-on-yl, benzodioxolanyl and benzodioxane, each heteroaryl being substituted at 0-4 carbon atoms with a substituent independently selected at each occurrence from the group C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, Br, F, I, C<sub>1-4</sub> haloalkyl, -CN, NR<sup>2g</sup>R<sup>2h</sup>, nitro, -OR<sup>2m</sup>, -SH, -S(O)<sub>n</sub>R<sup>2n</sup>, COR<sup>2m</sup>, -CO<sub>2</sub>R<sup>2m</sup>, -OC(O)R<sup>2n</sup>, -NR<sup>2g</sup>COR<sup>2m</sup>, -N(COR<sup>2m</sup>)<sub>2</sub>, -NR<sup>2g</sup>CONR<sup>2o</sup>R<sup>2p</sup> and each heteroaryl being substituted at any nitrogen atom with 0-1 substituents selected from the group R<sup>2g</sup>, CO<sub>2</sub>R<sup>3a</sup>, COR<sup>3a</sup> and SO<sub>2</sub>R<sup>3a</sup> wherein,

R<sup>3a</sup> is selected from the group C<sub>1-6</sub> alkyl, C<sub>1-4</sub> cycloalkyl-C<sub>1-6</sub> alkyl and benzyl, each benzyl being substituted on the aryl moiety with 0-1 substituents selected from the group

C<sub>1-4</sub> alkyl, Br, Cl, F, I, C<sub>1-4</sub> haloalkyl, nitro, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> haloalkoxy, and dimethylamino;

R<sup>4</sup> and R<sup>5</sup> are independently selected at each occurrence  
5 from H, Br, Cl, F, I, -CN, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, C<sub>1-6</sub> alkyloxy, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, amino, C<sub>1-4</sub> alkylamino, (C<sub>1-4</sub> alkyl)<sub>2</sub> amino and phenyl, each phenyl is substituted with 0-3 groups selected from the group consisting of C<sub>1-7</sub>  
10 alkyl, C<sub>3-8</sub> cycloalkyl, Br, Cl, F, I, -C(O)H, C<sub>1-4</sub> haloalkyl, nitro, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> haloalkoxy, C<sub>1-4</sub> alkylthio, C<sub>1-4</sub> alkylsulfinyl, C<sub>1-4</sub> alkylsulfonyl, C<sub>1-6</sub> alkylamino and (C<sub>1-4</sub> alkyl)<sub>2</sub> amino and wherein R<sup>4</sup> and R<sup>5</sup> non-phenyl groups may be substituted with 0-5  
15 substituents selected from OH, halogen, -C(O)H, -OC<sub>1-6</sub>-alkyl and C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkyl, C<sub>3-7</sub> c-alkyl, C<sub>1-6</sub> alkyl(OH)<sub>n</sub>CO<sub>2</sub>R wherein R is H or C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkyl(OH)<sub>n</sub>, wherein n is 0-3 or R<sup>4</sup> and R<sup>5</sup> may join together to form a C<sub>3-6</sub> alkylene chain; with the proviso that the compounds of  
20 Formula I with R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> as specifically defined below are excluded:

(a) a compound of formula I wherein R<sup>1</sup> is unsubstituted, unbranched (linear) C<sub>1-3</sub> alkyl and R<sup>2</sup> is -C(O)-Ph (EP 0 129  
25 847 A2, US 4,521,422, US 4,654,347);

(b) a compound of formula I, wherein R<sup>5</sup> is H or C<sub>1-3</sub> alkyl and R<sup>3</sup> is pyridyl, pyridyl-N-oxide, thien-3-yl or furan-3-yl or C<sub>1-3</sub> alkyl substituted versions thereof and R<sup>1</sup> is carboamoyl or unsubstituted, unbranched C<sub>1-3</sub> alkyl, R<sup>2</sup> is  
30 F, Cl, Br, formyl, carboxyl, CN, hydroxymethyl, unsubstituted, unbranched C<sub>1-3</sub> alkyl, -C(O)R, -C(O)OR, -CH<sub>2</sub>OR, -C(O)O(CH<sub>2</sub>)<sub>2</sub>OR, -C(O)O(CH<sub>2</sub>)<sub>2</sub>NHR, or -C(O)O(CH<sub>2</sub>)<sub>2</sub>NR<sup>2</sup> wherein R is C<sub>1-3</sub> alkyl (US 4,281,000);



- (c) a compound of formula I, wherein  $R^1$  is unsubstituted, unbranched  $C_{1-3}$  alkyl and  $R^2$  is halogen, CN or  $-C(O)R$  wherein R is H,  $C_{1-3}$  alkyl or  $C_{1-4}$  alkoxy,  $R^3$  is Ph substituted with  $NR^{2m}C(O)R^{2m}$  (US 4,626,538)
- 5 (d) a compound of formula I,  $R^2$  is CN, halogen,  $CO_2R$  with R equal to  $C_{1-3}$  alkyl, unsubstituted, unbranched  $C_{1-3}$  alkyl,  $C_{1-3}$  haloalkyl or  $CONH_2$  and  $R^1$  is equal to OR, SR wherein R is  $C_{1-3}$  alkyl,  $C_{1-4}$  haloalkyl or  $C_{3-4}$  halocycloalkyl, and  $R^3$  is phenyl or substituted phenyl (US
- 10 5,127,936);
- (e) a compound of formula I, wherein  $R^5$  is H or  $C_{1-3}$  alkyl;  $R^3$  is phenyl, ortho-trifluoromethylphenyl, meta-trifluorophenyl or meta-methoxyphenyl;  $R^1$  is carbamoyl or unsubstituted  $C_{1-3}$  alkyl;  $R^2$  is halogen, formyl, carboxyl,
- 15 cyano, hydroxymethyl, unsubstituted, unbranched  $C_{1-3}$  alkyl,  $-C(O)R$ ,  $-C(O)OR$ ,  $CH_2OR$ ,  $-C(O)O(CH_2)_2OR$ ,  $-C(O)O(CH_2)_2NHR$  or  $-C(O)O(CH_2)_2NR^2$  wherein R is  $C_{1-3}$  alkyl (US 4,178,449);
- (f) no entry
- 20 (g) in a compound of formula I,  $R^2$  is CN,  $R^1$  is methyl,  $R^4$  and  $R^5$  are H,  $R^3$  is phenyl substituted with imidazo (or 2-methylimidazo) through the imidazo nitrogen atom (Registry Reference 20, 21);
- (h) in a compound of formula I,  $R^2$  is CN,  $R^1$  is  $SCH_3$ ,  $R^3$
- 25 is para-chlorophenyl,  $R^4$  is  $SCH_3$  and  $R^5$  is H (registry reference 25);
- (i) in a compound of formula I,  $R^2$  is CN,  $R^1$  is  $SCH_3$ ,  $R^3$  is pyrid-4-yl,  $R^4$  is  $SCH_3$  and  $R^5$  is H (Registry Reference 26);
- (j) in a compound of formula I,  $R^2$  is CN,  $R^1$  is  $SCH_3$ ,  $R^3$  is
- 30 Ph,  $R^4$  is  $SCH_3$  and  $R^5$  is H (Registry Reference 27);
- (k) in a compound of formula I,  $R^2$  is  $C(O)NH_2$ ,  $R^1$  is  $SCH_3$ ,  $R^3$  is pyrid-3-yl,  $R^4$  is  $SCH_3$  and  $R^5$  is H (Registry Reference 28);

- (l) in a compound of formula I,  $R^2$  is  $C(O)NH_2$ ,  $R^1$  is  $SCH_3$ ,  $R^3$  is Ph,  $R^4$  is  $SCH_3$  (or Ph) and  $R^5$  is H (Registry Reference 29, 31);
- (m) in a compound of formula I,  $R^2$  is  $C(O)OEt$ ,  $R^1$  is  $SCH_3$ ,  $R^3$  is Ph,  $R^4$  is  $SCH_3$  (or Ph) and  $R^5$  is H (registry reference 30, 32);
- (n) in a compound of formula I,  $R^1$  is  $N(C(O)CH_3)_2$ ,  $R^2$  is  $CH_2Ph(p-Me, p-Cl)$ ,  $R^3$  is Ph (p-ClPh),  $R^4$  is  $SCH_3$  and  $R^5$  is H (Registry Reference 33, 34);
- 10 (o) in a compound of formula I,  $R^1$  is  $N(C(O)CH_3)_2$ ,  $R^2$  is  $CH_2Ph(p-OMe)$ ,  $R^3$  is p-ClPh,  $R^4$  is  $SCH_3$  and  $R^5$  is H (registry ref. 35);
- (p) in a compound of formula I,  $R^2$  is CN,  $R^1$  is  $CH_3$ ,  $R^3$  is Ph,  $R^4$  is H and  $R^5$  is H (registry ref. 44);
- 15 (q) in a compound of formula I,  $R^2$  is  $C(O)NH_2$ ,  $R^1$  is  $CH_3$ ,  $R^3$  is Ph,  $R^4$  is  $CH_3$  and  $R^5$  is H (reg. ref. 45);
- (s) in a compound of formula I,  $R^2$  is  $C(O)NH_2$ ,  $R^1$  is  $CH_3$ ,  $R^3$  is pyrid-4-yl,  $R^4$  and  $R^5$  are H (reg. ref. 46);
- (t) in a compound of formula I,  $R^2$  is  $C(O)NH_2$ ,  $R^1$  is  $CH_3$ ,  $R^3$  is m- $CF_3Ph$ ,  $R^4$  and  $R^5$  are H (reg. ref. 47);
- 20 (u) in a compound of formula I,  $R^2$  is CN,  $R^1$  is  $CH_3$ ,  $R^3$  is Ph,  $R^4$  is  $CH_3$  and  $R^5$  is H (reg. ref. 48);
- (v) in a compound of formula I,  $R^2$  is CN,  $R^1$  is  $CH_3$ ,  $R^3$  is pyrid-4-yl,  $R^4$  and  $R^5$  are H (reg. ref. 49);
- 25 (w) no entry
- (x) in a compound of formula I,  $R^2$  is  $CH_3$ ,  $R^1$  is  $CH_3$ ,  $R^3$  is p-F-Ph,  $R^4$  is c-propyl and  $R^5$  is  $CH=CH-CH(OH)CH_2CH(OH)CH_2C(O)O-iPr$  (reg. ref. 75);
- (y) in a compound of formula I,  $R^2$  is  $CH_3$ ,  $R^1$  is  $CH_3$ ,  $R^3$  is p-F-Ph,  $R^4$  is c-propyl and  $R^5$  is  $CH=CH-CH(OH)CH_2CH(OH)CH_2C(O)O-nPr$  (reg. ref. 76);
- 30

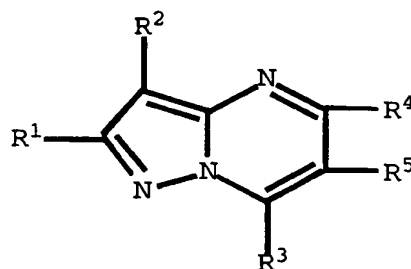
- (z) in a compound of formula I,  $R^2$  is  $CH_3$ ,  $R^1$  is  $CH_3$ ,  $R^3$  is p-F-Ph,  $R^4$  is c-propyl and  $R^5$  is  $CH=CH-CH(OH)CH_2CH(OH)CH_2C(O)OMe$  (reg. ref. 77);
- (aa) in a compound of formula I,  $R^2$  is  $CH_3$ ,  $R^1$  is  $CH_3$ ,  $R^3$  is p-F-Ph,  $R^4$  is c-propyl and  $R^5$  is  $CH=CH-CH(OH)CH_2CH(OH)CH_2C(O)OH$  (reg. ref. 78);
- (bb) in a compound of formula I,  $R^2$  is  $CH_3$ ,  $R^1$  is  $CH_3$ ,  $R^3$  is p-F-Ph,  $R^4$  is c-propyl and  $R^5$  is  $-CH_2OH$  (reg. ref. 100);
- (cc) in a compound of formula I,  $R^2$  is  $CH_3$ ,  $R^1$  is  $CH_3$ ,  $R^3$  is p-F-Ph,  $R^4$  is c-propyl and  $R^5$  is  $-C(O)H$  (reg. ref. 105);
- (dd) in a compound of formula I,  $R^2$  is  $CH_3$ ,  $R^1$  is  $CH_3$ ,  $R^3$  is p-F-Ph,  $R^4$  is c-propyl and  $R^5$  is  $-CH=CH-C(O)H$  (reg. ref. 110);
- (ee) in a compound of formula I,  $R^2$  is  $CH_3$ ,  $R^1$  is  $CH_3$ ,  $R^3$  is p-F-Ph,  $R^4$  is c-propyl and  $R^5$  is  $CH=CH-CH(OH)CH_2CH(OH)CH_2C(O)OEt$  (reg. ref. 115);
- (ff) in a compound of formula I,  $R^2$  is  $CH_3$ ,  $R^1$  is  $CH_3$ ,  $R^3$  is p-F-Ph,  $R^4$  is c-propyl and  $R^5$  is  $CH=CH-CH(OH)CH_2CH(OH)CH_2C(O)O^-Na^+$  (reg. ref. 120);
- (gg) in a compound of formula I,  $R^2$  is CN,  $R^1$  is  $CF_3$ ,  $R^3$  is m-Cl-Ph,  $R^4$  is  $CH_3$  and  $R^5$  is H (reg. ref. 130);
- (hh) in a compound of formula I,  $R^2$  is CN,  $R^1$  is  $CF_3$ ,  $R^3$  is m- $CF_3$ -Ph,  $R^4$  is  $CH_3$  and  $R^5$  is H (reg. ref. 132);
- (ii) in a compound of formula I,  $R^2$  is CN,  $R^1$  is  $CF_3$ ,  $R^3$  is Ph,  $R^4$  is  $CH_3$  and  $R^5$  is H (reg. ref. 133);
- (jj)-(mm) no entry
- (nn) in a compound of formula I,  $R^2$  is  $-C(O)NH_2$ ,  $R^1$  is Me,  $R^3$  is Ph,  $R^4$  is H and  $R^5$  is Me (reg. ref. 140);
- (oo) in a compound of formula I,  $R^2$  is CN,  $R^1$  is Me,  $R^3$  is Ph,  $R^4$  is H and  $R^5$  is Me (reg. ref. 141);
- (pp) in a compound of formula I,  $R^2$  is CN,  $R^1$  is Me,  $R^3$  is o-Cl,m-Cl-Ph,  $R^4$  is H and  $R^5$  is H (reg. ref. 144);

- (qq) in a compound of formula I,  $R^2$  is  $C(O)NH_2$ ,  $R^1$  is  $CH_3$ ,  $R^3$  is Ph,  $R^4$  and  $R^5$  are H (reg. ref. 145);
- (rr) in a compound of formula I,  $R^2$  is  $C(O)NH_2$ ,  $R^1$  is  $CH_3$ ,  $R^3$  is 0-CL,m-Cl-Ph,  $R^4$  and  $R^5$  are H (reg. ref. 146);
- 5 (ss) in a compound of formula I,  $R^2$  is  $C(O)OMe$ ,  $R^1$  is -  
SCH<sub>2</sub>-Ph,  $R^3$  is Ph,  $R^4$  is Me and  $R^5$  is H (reg. ref. 147);
- (tt) in a compound of formula I,  $R^2$  is  $C(O)OMe$ ,  $R^1$  is -  
SCH<sub>2</sub>-Ph,  $R^3$  is Ph,  $R^4$  is H and  $R^5$  is H (reg. ref. 148);
- (uu) in a compound of formula I,  $R^2$  is  $C(O)Ph$ ,  $R^1$  is Me,  $R^3$   
10 is pyrid-4-yl,  $R^4$  and  $R^5$  are H (reg. ref. 154);
- (vv) in a compound of formula I,  $R^2$  is  $C(O)Ph$ ,  $R^1$  is Me,  $R^3$   
is m-CF<sub>3</sub>-Ph,  $R^4$  and  $R^5$  are H (reg. ref. 155);
- (ww) in a compound of formula I,  $R^2$  is  $C(O)Ph$ ,  $R^1$  is Me,  $R^3$   
is pyrid-3-yl,  $R^4$  and  $R^5$  are H (reg. ref. 156);
- 15 (xx) in a compound of formula I,  $R^2$  is CN,  $R^1$  is SCH<sub>3</sub>,  $R^3$   
is Ph,  $R^4$  is Ph and  $R^5$  is H (reg. ref. 157);
- (yy) in a compound of formula I,  $R^2$  is CN,  $R^1$  is SCH<sub>3</sub>,  $R^3$   
is Ph,  $R^4$  is Ph and  $R^5$  is H (reg. ref. 157);
- (zz) in a compound of formula I,  $R^2$  is Cl,  $R^1$  is Et,  $R^3$  is  
20 pyrid-3-yl,  $R^4$  and  $R^5$  are H (reg. ref. 163);
- (aaa) in a compound of formula I,  $R^2$  is CO<sub>2</sub>H,  $R^1$  is Et,  $R^3$   
is pyrid-3-yl,  $R^4$  and  $R^5$  are H (reg. ref. 164);
- (bbb) in a compound of formula I,  $R^2$  is CO<sub>2</sub>H,  $R^1$  is CH<sub>3</sub>,  $R^3$   
is pyrid-3-yl,  $R^4$  and  $R^5$  are H and H Cl salt (reg. ref.  
25 165);
- (ccc) in a compound of formula I,  $R^2$  is  $C(O)OEt$ ,  $R^1$  is CH<sub>3</sub>,  
 $R^3$  is pyrid-3-yl,  $R^4$  and  $R^5$  are H (reg. ref. 166);
- (ddd) in a compound of formula I,  $R^2$  is CN,  $R^1$  is CH<sub>3</sub>,  $R^3$   
is pyrid-3-yl,  $R^4$  is H and  $R^5$  is CH<sub>3</sub> (reg. ref. 167);
- 30 (eee) in a compound of formula I,  $R^2$  is CN,  $R^1$  is CH<sub>3</sub>,  $R^3$   
is pyrid-3-yl,  $R^4$  and  $R^5$  are H (reg. ref. 168);
- (fff) in a compound of formula I,  $R^2$  is  $C(O)OEt$ ,  $R^1$  is Et,  
 $R^3$  is pyrid-3-yl,  $R^4$  and  $R^5$  are H (reg. ref. 169);

27

- (ggg) in a compound of formula I,  $R^2$  is CN,  $R^1$  is Et,  $R^3$  is pyrid-3-yl,  $R^4$  and  $R^5$  are H (reg. ref. 170);
- (hhh) in a compound of formula I,  $R^2$  is CN,  $R^1$  is  $CH_3$ ,  $R^3$  is m- $CF_3$ -Ph,  $R^4$  and  $R^5$  are H (reg. ref. 172);
- 5 (iii) in a compound of formula I,  $R^2$  is CN,  $R^1$  is  $CH_2CN$ ,  $R^3$  is m- $CF_3$ -Ph,  $R^4$  and  $R^5$  are H (reg. ref. 173);
- (jjj) in a compound of formula I,  $R^2$  is C(O)OMe,  $R^1$  is Me,  $R^3$  is m- $CF_3$ -Ph,  $R^4$  and  $R^5$  are H (reg. ref. 174);
- (kkk) in a compound of formula I,  $R^2$  is CN,  $R^1$  is Et,  $R^3$  is
- 10 m-OMe-Ph,  $R^4$  and  $R^5$  are H (reg. ref. 175);
- (lll) in a compound of formula I,  $R^2$  is C(O)OEt,  $R^1$  is Et,  $R^3$  is Ph,  $R^4$  and  $R^5$  are H (reg. ref. 176);
- (mmm) in a compound of formula I,  $R^2$  is C(O)OEt,  $R^1$  is Et,  $R^3$  is m- $CF_3$ -Ph,  $R^4$  and  $R^5$  are H (reg. ref. 177);
- 15 (nnn) in a compound of formula I,  $R^2$  is CN,  $R^1$  is Et,  $R^3$  is m- $CF_3$ -Ph,  $R^4$  is H and  $R^5$  is  $CH_3$  (reg. ref. 178);
- (ooo) in a compound of formula I,  $R^2$  is CN,  $R^1$  is Et,  $R^3$  is m- $CF_3$ ,  $R^4$  and  $R^5$  are H (reg. ref. 179);
- (ppp) in a compound of formula I,  $R^2$  is CN,  $R^1$  is C(O)NH<sub>2</sub>,
- 20  $R^3$  is m- $CF_3$ -Ph,  $R^4$  and  $R^5$  are H (reg. ref. 180);
- (qqq) in a compound of formula I,  $R^2$  is CN,  $R^1$  is Et,  $R^3$  is Ph,  $R^4$  and  $R^5$  are H (reg. ref. 181).

- [1'] In a preferred embodiment, the present
- 25 invention provides a novel compound of formula I:



(I)

or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

- 5  $R^1$  is selected from the group consisting of
- $C_{1-6}$  alkyl,
- $C_{2-10}$  alkenyl,
- $C_{2-10}$  alkynyl,
- 10  $C_{3-6}$  cycloalkyl,
- $C_{1-6}$  alkyloxy,
- $C_{1-6}$  alkylS(O)<sub>n</sub>,
- $-NR^{1a}R^{1b}$  wherein  $R^{1a}$  and  $R^{1b}$  are independently selected from
- H,  $C_{1-4}$  alkyl,  $-C(O)C_{1-4}$ alkyl,
- 15  $-C(O)NR^{1a}R^{1b}$ ,
- $-O-C(O)C_{1-4}$ alkyl,
- $-XR^{1c}$  wherein  $R^{1c}$  is selected from H or  $-C_{1-4}$  alkylaryl;
- X is selected from O or S(O)<sub>n</sub>,
- 20
- wherein  $R^1$  is substituted with 0-6 substituents selected from halogen,  $C_{1-4}$  alkyl,  $C_{1-6}$  alkyloxy,  $C_{1-4}$  haloalkyl,  $-NR^{1a}R^{1b}$ ,  $-XR^{1c}$ ;
- 25  $R^2$  is selected from the group consisting of
- $C_{1-10}$  alkyl excluding unsubstituted, unbranched  $C_{1-3}$ alkyl,
- $C_{2-10}$  alkenyl,
- $C_{2-10}$  alkynyl,
- $C_{3-8}$  cycloalkyl,
- 30  $C_{3-6}$  cycloalkyl  $C_{1-6}$  alkyl,
- $C_{1-10}$  alkyloxy,
- $C_{1-10}$  alkyloxy $C_{1-10}$  alkyl,
- $C_{1-4}$  alkoxy  $C_{1-4}$  alkyl,

-SO<sub>2</sub>-C<sub>1-10</sub>alkyl

-SO<sub>2</sub>R<sup>2a</sup> wherein R<sup>2a</sup> is aryl,

-SO<sub>2</sub>R<sup>2b</sup> wherein R<sup>2b</sup> is heteroaryl,

5 -NR<sup>2c</sup>R<sup>2d</sup> wherein R<sup>2c</sup> and R<sup>2d</sup> are independently selected from  
 H, C<sub>1-8</sub> alkyl, S(O)<sub>n</sub>C<sub>1-4</sub> alkyl, C(O)NR<sup>2c</sup>R<sup>2d</sup>, CO<sub>2</sub>C<sub>1-4</sub>alkyl,  
 C<sub>3-8</sub> cycloalkyl, C<sub>1-6</sub> alkyloxyC<sub>1-6</sub> alkyl, -C(O)C<sub>1-4</sub>alkyl  
 or R<sup>2c</sup> and R<sup>2d</sup> may join to form a heterocyclic ring  
 having 0-3 heteroatoms selected from O, N or S,

10

n is 0, 1 or 2;

R<sup>2</sup> is substituted with 0-3 substituents independently  
 selected from R', R'', R''' wherein R', R'' and R''' are  
 15 independently selected from C<sub>1-6</sub> alkyl, C<sub>3-7</sub> cycloalkyl,  
 hydroxyC<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkyloxyC<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>1-6</sub>  
 alkyloxy, hydroxy, or

R<sup>2</sup> is substituted with 0-3 substituents independently  
 20 selected from:

-CN,

-S(O)<sub>n</sub>R<sup>2e</sup> wherein R<sup>2e</sup> is selected from C<sub>1-4</sub> alkyl, C<sub>1-4</sub>  
 haloalkyl, C<sub>1-4</sub> alkyloxy C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl;

25 -COR<sup>2f</sup> wherein R<sup>2f</sup> is selected from H, C<sub>1-4</sub> alkyl, C<sub>1-4</sub>  
 haloalkyl, C<sub>1-4</sub> alkyloxy C<sub>1-4</sub> alkyl, C<sub>3-6</sub>  
 cycloalkyl, and C<sub>3-6</sub> cycloalkylC<sub>1-4</sub> alkyl;

-CO<sub>2</sub>R<sup>2f</sup>,

30 -NR<sup>2g</sup>COR<sup>2f</sup> wherein R<sup>2g</sup> is selected from H, C<sub>1-6</sub> alkyl, C<sub>3-7</sub> c-  
 alkyl, C<sub>3-6</sub> cycloalkyl C<sub>1-6</sub> alkyl;

-N(COR<sup>2f</sup>)<sub>2</sub>,

-NR<sup>2g</sup>CONR<sup>2f</sup>R<sup>2h</sup>, wherein R<sup>2h</sup> is selected from H, C<sub>1-6</sub> alkyl,

C<sub>1-4</sub> haloalkyl, C<sub>1-4</sub> alkoxy C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl and C<sub>3-6</sub> cycloalkylC<sub>1-6</sub> alkyl;

- 5 -NR<sup>2g</sup>CO<sub>2</sub>R<sup>2e</sup>,  
 -CONR<sup>2g</sup>R<sup>2h</sup>,  
 1-morpholinyl,  
 1-piperidinyl,  
 1-piperazinyl,
- 10 and  
 C<sub>3-8</sub> cycloalkyl wherein 0-1 carbon atoms in the C<sub>4-8</sub> cycloalkyl is replaced by a group selected from  
 -O-, -S(O)<sub>n</sub>-, -NR<sup>2g</sup>-, -NCO<sub>2</sub>R<sup>2e</sup>, -NCOR<sup>2e</sup>,  
 and -NSO<sub>2</sub>R<sup>2e</sup>; and wherein N<sub>4</sub> in
- 15 1-piperazinyl is substituted with 0-1  
 substituents selected from R<sup>2g</sup>, CO<sub>2</sub>R<sup>2e</sup>, COR<sup>2e</sup> and  
 SO<sub>2</sub>R<sup>2e</sup>; or
- the group R<sup>2j</sup>, R<sup>2k</sup>, C<sub>1-6</sub> alkyl, C<sub>2-8</sub>
- 20 alkenyl, C<sub>2-8</sub> alkynyl, Br, Cl, F, I, C<sub>1-4</sub> haloalkyl, -OR<sup>2g</sup>,  
 -NR<sup>2g</sup>R<sup>2h</sup>, -C<sub>1-6</sub> alkylOR<sup>2g</sup>, and C<sub>3-8</sub> cycloalkyl which is  
 substituted with 0-1 R<sup>21</sup> and in which 0-1 carbons of C<sub>4-8</sub>  
 cycloalkyl is replaced by -O-, wherein
- 25 R<sup>2j</sup> is selected from heteroaryl wherein heteroaryl  
 includes pyridyl, pyrimidinyl, triazinyl, furanyl,  
 quinolinyl, isoquinolinyl, thienyl, imidazolyl,  
 thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl,  
 benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl,
- 30 pyrazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-  
 dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, 2,3-  
 dihydrobenzothienyl-s-oxide, 2,3-dihydro-benzothienyl-S-  
 dioxide, indolinyl, benzoxazolin-2-onyl, benzodioxolanyl



31

- and benzodioxane, each heteroaryl being substituted on 0-4 carbon atoms with a substituent independently selected from the group  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl, Br, Cl, F, I,  $C_{1-4}$  haloalkyl, -CN, nitro,  $OR^{2m}$ , -SH,  $-S(O)_nR^{2h}$ ,  $-COR^{2m}$ , -
- 5  $OC(O)R^{2h}$ ,  $-NR^{2g}COR^{2m}$ ,  $-N(COR^{2m})_2$ ,  $-NR^{2g}CONR^{2o}R^{2p}$ ,  $-NR^{2g}CO_2R^{2h}$ , -  
 $NR^{2o}R^{2p}$  and  $-CONR^{2o}R^{2p}$  and each heteroaryl being substituted on any nitrogen atom with 0-1 substituents selected from the group  $R^{2g}$ ,  $CO_2R^{2e}$ ,  $COR^{2e}$  and  $SO_2R^{2e}$ ;
- 10  $R^{2k}$  is heterocyclyl which is a saturated or partially saturated heteroaryl as defined for  $R^{2j}$ , each heterocyclyl being substituted on 0-4 carbon atoms with a substituent independently selected from the group  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl, Br, Cl, F, I,  $C_{1-4}$  haloalkyl, -CN, nitro,  $-OR^{2m}$ ,
- 15  $-SH$ ,  $-S(O)_nR^{2h}$ ,  $-COR^{2m}$ ,  $-OC(O)R^{2h}$ ,  $-NR^{2g}COR^{2m}$ ,  $-N(COR^{2m})_2$ ,  
 $-NR^{2g}CONR^{2o}R^{2p}$ ,  $NR^{2g}CO_2R^{2h}$ ,  $-NR^{2o}R^{2p}$  and  $-CONR^{2o}R^{2p}$  and each heterocyclyl being substituted on any nitrogen atom with 0-1 substituents selected from the group  $R^{2f}$ ,  $CO_2R^{2e}$ ,  $COR^{2e}$  and  $SO_2R^{2e}$ ;
- 20 wherein
- $R^{21}$  is H,  $C_{1-4}$  alkyl,  $C_{3-6}$  cycloalkyl- $C_{1-4}$  alkyl and  $C_{3-8}$  cycloalkyl;
- 25  $R^{2m}$  is H,  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl  $C_{1-6}$  alkyl,  $C_{1-2}$  alkyloxy  $C_{1-2}$  alkyl,  $C_{1-4}$  haloalkyl,  $R^{2g}S(O)_n-C_{1-4}$  alkyl and  $R^{2r}R^{2s}N-C_{2-4}$  alkyl;
- 30  $R^{2n}$  is H,  $C_{1-6}$  alkyl,  $C_{3-10}$  cycloalkyl,  $C_{3-6}$  cycloalkyl- $C_{1-6}$  alkyl,  $C_{1-2}$  alkyloxy  $C_{1-2}$  alkyl, and  $C_{1-4}$  haloalkyl;

$R^{2o}$  and  $R^{2p}$  are independently selected at each occurrence from H,  $C_{1-6}$  alkyl,  $C_{3-10}$  cycloalkyl,  $C_{3-6}$  cycloalkyl  $C_{1-6}$  alkyl and  $C_{1-4}$  haloalkyl;

- 5  $R^{2q}$  is selected from  $C_{1-6}$  alkyl,  $C_{1-4}$  haloalkyl,  $C_{1-4}$  alkoxy-  
 $C_{1-4}$  alkyl,  $C_{3-6}$  cycloalkyl,  $C_{3-6}$  cycloalkyl-  $C_{1-6}$  alkyl, aryl,  
 aryl( $C_{1-4}$  alkyl), heteroaryl and heteroaryl ( $C_{1-4}$  alkyl)-  
 and benzyl, each benzyl being substituted on the aryl  
 moiety with 0-1 substituents selected from the group  $C_{1-4}$   
 10 alkyl, Br, Cl, F, I,  $C_{1-4}$  haloalkyl, nitro,  $C_{1-4}$  alkoxy  $C_{1-4}$   
 haloalkoxy, and dimethylamino;

- $R^{2r}R^{2s}$  taken together with the N form 1-pyrrolidinyl, 1-  
 morpholinyl, 1-piperidinyl or 1-piperazinyl wherein N<sub>4</sub> in  
 15 1-piperiazinyl is substituted with 0-1 substituents  
 selected from the group  $R^{2t}$ ,  $CO_2R^{2q}$ ,  $COR^{2q}$  and  $SO_2R^{2q}$ ;

- $R^{2t}$  is selected from H,  $C_{1-4}$  alkyl,  $C_{1-4}$  haloalkyl,  $C_{1-4}$  alkoxy  
 $-C_{1-4}$  alkyl,  $C_{3-6}$  cycloalkyl,  $C_{3-6}$  cycloalkyl -  $C_{1-6}$  alkyl,  
 20 aryl, aryl ( $C_{1-4}$  alkyl)-, heteroaryl and heteroaryl ( $C_{1-4}$   
 alkyl);

- $R^3$  is selected from an aryl or heteroaryl group attached  
 through an unsaturated carbon atom;

- 25 aryl is selected from phenyl, naphthyl, indanyl and  
 indenyl, each aryl being substituted with 0-5  
 substituents independently selected at each occurrence  
 from  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl, methylenedioxy,  $C_{1-4}$   
 30 alkyloxy- $C_{1-4}$  alkyloxy,  $-OR^{2m}$ , Br, Cl, F, I,  $C_{1-4}$  haloalkyl,  
 $-CN$ ,  $-NO_2$ ,  $-SH$ ,  $-S(O)_nR^{2n}$ ,  $-COR^{2m}$ ,  $-CO_2R^{2m}$ ,  $-OC(O)R^{2n}$ , -  
 $NR^{2q}COR^{2m}$ ,  $-N(COR^{2m})_2$ ,  $-NR^{2q}CONR^{2o}R^{2p}$ ,  $-NR^{2q}CO_2R^{2h}$ ,  $-NR^{2o}R^{2p}$  and  
 $CONR^{2o}R^{2p}$  and up to 1 phenyl, each phenyl substituent being

substituted with 0-4 substituents selected from the group  $C_{1-3}$  alkyl,  $C_{1-3}$  alkoxy, Br, Cl, F, I, -CN, dimethylamino,  $CF_3$ ,  $C_2F_5$ ,  $OCF_3$ ,  $SO_2Me$  and acetyl;

- 5 heteroaryl is selected from the group pyridyl, pyrimidyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-
- 10 dihydrobenzo-furanyl, 2,3-dihydrobenzothienyl, 2,3-dihydro-benzothienyl-S-oxide, 2,3-dihydrobenzothienyl-s-dioxide, indolinyl, benzoxazolin-2-on-yl, benzodioxolanyl and benzodioxane, each heteroaryl being substituted at 0-4 carbon atoms with a substituent independently selected at
- 15 each occurrence from the group  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl, Br, F, I,  $C_{1-4}$  haloalkyl, -CN,  $NR^{2g}R^{2h}$ , nitro,  $-OR^{2m}$ , -SH,  $-S(O)_nR^{2n}$ ,  $COR^{2m}$ ,  $-CO_2R^{2m}$ ,  $-OC(O)R^{2n}$ ,  $-NR^{2g}COR^{2m}$ ,  $-N(COR^{2m})_2$ ,  $-NR^{2g}CONR^{2o}R^{2p}$  and each heteroaryl being substituted at any nitrogen atom with 0-1 substituents selected from the
- 20 group  $R^{2g}$ ,  $CO_2R^{3a}$ ,  $COR^{3a}$  and  $SO_2R^{3a}$  wherein,

- $R^{3a}$  is selected from the group  $C_{1-6}$  alkyl,  $C_{1-4}$  cycloalkyl- $C_{1-6}$  alkyl and benzyl, each benzyl being substituted on the aryl moiety with 0-1 substituents selected from the group
- 25  $C_{1-4}$  alkyl, Br, Cl, F, I,  $C_{1-4}$  haloalkyl, nitro,  $C_{1-4}$  alkoxy,  $C_{1-4}$  haloalkoxy, and dimethylamino;

- $R^4$  and  $R^5$  are independently selected at each occurrence from H, Br, Cl, F, I, -CN,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{3-6}$  cycloalkyl,  $C_{1-6}$  alkyloxy,  $C_{1-6}$  alkylthio,  $C_{1-6}$  alkylsulfanyl,  $C_{1-6}$  alkylsulfonyl, amino,  $C_{1-4}$  alkylamino,  $(C_{1-4} \text{ alkyl})_2$  amino and phenyl, each phenyl is substituted with 0-3 groups selected from the group consisting of  $C_{1-}$
- 30

alkyl, C<sub>3-8</sub> cycloalkyl, Br, Cl, F, I, -C(O)H, C<sub>1-4</sub> haloalkyl, nitro, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> haloalkoxy, C<sub>1-4</sub> alkylthio, C<sub>1-4</sub> alkylsulfinyl, C<sub>1-4</sub> alkylsulfonyl, C<sub>1-6</sub> alkylamino and (C<sub>1-4</sub> alkyl)<sub>2</sub> amino and wherein R<sup>4</sup> and R<sup>5</sup> non-phenyl groups may be substituted with 0-5 substituents selected from OH, halogen, -C(O)H, -OC<sub>1-6</sub>-alkyl and C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkyl, C<sub>3-7</sub> c-alkyl, C<sub>1-6</sub> alkyl(OH)<sub>n</sub>CO<sub>2</sub>R wherein R is H or C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkyl(OH)<sub>n</sub>, wherein n is 0-3 or R<sup>4</sup> and R<sup>5</sup> may join together to form a C<sub>3-6</sub> alkylene chain.

[2] The present invention relates to a compound as described directly above in [1] or [1'] wherein

15 R<sup>1</sup> is selected from C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkylthio, -XR<sup>1c</sup> wherein R<sup>1</sup> is substituted with 0-6 substituents selected from halogen, C<sub>1-4</sub> alkyl or C<sub>1-4</sub> haloalkyl;

R<sup>2</sup> is selected from substituted-C<sub>1-10</sub> alkyl, branched C<sub>3-10</sub> alkyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, C<sub>3-6</sub> cycloalkyl C<sub>1-6</sub> alkyl, -NR<sup>2c</sup>R<sup>2d</sup> wherein, in the case of substituted-C<sub>1-10</sub> alkyl, 1-3 substituents are independently selected from the group R<sup>2i</sup>, R<sup>2j</sup>, R<sup>2k</sup>, C<sub>1-6</sub> alkyl, C<sub>2-8</sub> alkenyl, C<sub>2-8</sub> alkynyl, Br, Cl, F, I, C<sub>1-4</sub> haloalkyl, -OR<sup>2g</sup>, -NR<sup>2g</sup>R<sup>2h</sup>, -C<sub>1-6</sub> alkylOR<sup>2g</sup>, and C<sub>3-8</sub> cycloalkyl which is substituted with 0-1 R<sup>2i</sup> and in which 0-1 carbons of C<sub>4-8</sub> cycloalkyl is replaced by -O- and wherein the R<sup>2</sup> groups, other than substituted-C<sub>1-10</sub> alkyl, are substituted with 0-3 substituents independently selected from the

20 group R<sup>2i</sup>, R<sup>2j</sup>, R<sup>2k</sup>, C<sub>1-6</sub> alkyl, C<sub>2-8</sub> alkenyl, C<sub>2-8</sub> alkynyl, Br, Cl, F, I, C<sub>1-4</sub> haloalkyl, -OR<sup>2g</sup>, -NR<sup>2g</sup>R<sup>2h</sup>, -C<sub>1-6</sub> alkylOR<sup>2g</sup>, and C<sub>3-8</sub> cycloalkyl which is substituted with 0-1 R<sup>2i</sup> and in which 0-1 carbons of C<sub>4-8</sub> cycloalkyl is replaced by -O-.

35

[3] The present invention also relates to a compound described in groups [1], [1'] or [2] wherein R<sup>3</sup> is selected from an aryl group selected from phenyl or substituted versions thereof or a heteroaryl group selected from pyridyl or substituted versions thereof.

[4] The present invention relates to a compound described directly above in groups [1'] and [1]-[3] wherein R<sup>3</sup> is substituted with 0-4 substituents independently selected from halogen, C<sub>1-4</sub> alkyloxy, C<sub>1-6</sub> alkyl or NR'R'' wherein R' and R'' are independently selected from H or C<sub>1-6</sub> alkyl.

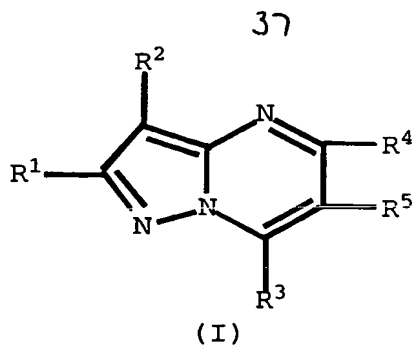
[5] The present invention preferably relates to a compound as described directly above in groups [1'] and [1]-[4] wherein R<sup>3</sup> is selected from 2,4-dichlorophenyl, 2-chloro-4-methoxyphenyl, 2,4,6-trimethylphenyl, 2,4,6-trimethoxyphenyl, 2-dimethylamino-4-methyl-pyridin-5-yl, 2,4-dichloro-5-fluorophenyl, 2-chloro-4-methoxy-5-fluorophenyl, 2-chloro-4,5-dimethoxyphenyl or 2-chloro-4,5-dimethoxyphenyl.

[6] The present invention also preferably relates to a compound as described in groups [1'] and [2]-[5] wherein R<sup>2</sup> is selected from C<sub>1</sub> alkyl of the formula -CR'R'' wherein R', R'' and R''' are independently selected from H, C<sub>1-6</sub> alkyl, C<sub>3-7</sub> cycloalkyl, hydroxyC<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkyloxyC<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>1-6</sub> alkyloxy, hydroxy, with the proviso that each of R', R'' and R''' cannot be H;

or R<sup>2</sup> is selected from NR<sup>2c</sup>R<sup>2d</sup> wherein R<sup>2c</sup> and R<sup>2d</sup> are independently selected from H or C<sub>1-6</sub> alkyl.

[7] The present invention preferably relates to a compound according to groups [1'] and [1]-[6] wherein  $R^3$  is selected from an aryl or heteroaryl group attached through an unsaturated carbon atom wherein, aryl is phenyl, each phenyl being substituted with 0-5 substituents independently selected at each occurrence from  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl, methylenedioxy,  $C_{1-4}$  alkyloxy- $C_{1-4}$  alkyloxy,  $-OR^{2m}$ , Br, Cl, F, I,  $C_{1-4}$  haloalkyl, -CN,  $-NO_2$ , -SH,  $-S(O)_nR^{2n}$ ,  $-COR^{2m}$ ,  $-CO_2R^{2m}$ ,  $-OC(O)R^{2n}$ ,  $-NR^{2g}COR^{2m}$ ,  $-N(COR^{2m})_2$ ,  $-NR^{2g}CONR^{2o}R^{2p}$ ,  $-NR^{2g}CO_2R^{2h}$ ,  $-NR^{2o}R^{2p}$  and  $CONR^{2o}R^{2p}$  and up to 1 phenyl, each phenyl substituent being substituted with 0-4 substituents selected from the group  $C_{1-3}$  alkyl,  $C_{1-3}$  alkoxy, Br, Cl, F, I, -CN, dimethylamino,  $CF_3$ ,  $C_2F_5$ ,  $OCF_3$ ,  $SO_2Me$  and acetyl and wherein, heteroaryl is selected at each occurrence from pyridyl, each pyridyl being substituted at 0-4 carbon atoms with a substituent independently selected at each occurrence from the group  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl, Br, F, I,  $C_{1-4}$  haloalkyl, -CN, nitro,  $-OR^{2m}$ , -SH,  $-S(O)_nR^{2n}$ ,  $COR^{2m}$ ,  $-CO_2R^{2m}$ ,  $-OC(O)R^{2n}$ ,  $-NR^{2g}COR^{2m}$ ,  $-N(COR^{2m})_2$ ,  $-NR^{2g}CONR^{2o}R^{2p}$  and each pyridyl being substituted at any nitrogen atom with 0-1 substituents selected from the group  $R^{2g}$ ,  $CO_2R^{3a}$ ,  $COR^{3a}$  and  $SO_2R^{3a}$ .

[8] The present invention preferably relates to a compound of formula (I)



or a pharmaceutically acceptable salt, stereoisomer or prodrug thereof, wherein

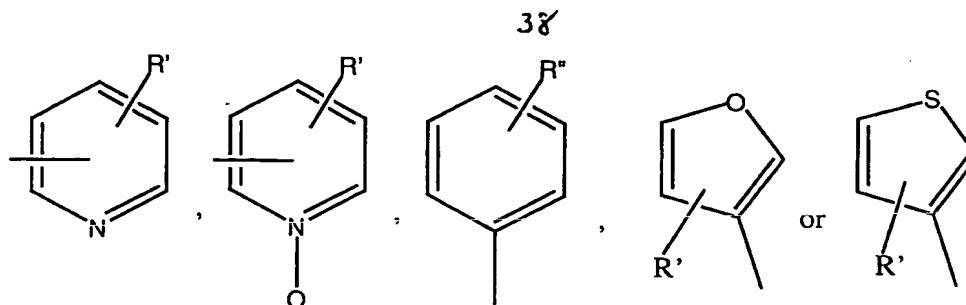
5  $R^1$  is selected from  $C_{1-6}$  alkyl,  $C_{1-6}$  alkyloxy, -SH or OH;

$R^2$  is selected from  $C_{1-4}$  alkyl which is unsubstituted or substituted with 1-4 substituents selected from  $C_{1-6}$  alkyl,  $C_{3-8}$  cycloalkyl,  $C_{1-6}$  alkylOR<sup>2g</sup>,  $C_{2-6}$  alkenyl or OR<sup>2g</sup>  
 10 wherein R<sup>2g</sup> is H or  $C_{1-6}$  alkyl;

$R^3$  is selected from an aryl or heteroaryl group bonded through an unsaturated carbon atom that is unsubstituted or substituted with 1-4 substituents selected from Cl, F, I, Br, -OH, CF<sub>3</sub>, S(O)<sub>n</sub> $C_{1-6}$  alkyl, -OC<sub>1-6</sub> alkyl,  $C_{1-6}$  alkyl or  
 15 NR<sup>2g</sup>R<sup>2h</sup> wherein R<sup>2g</sup> and R<sup>2h</sup> are independently selected from H or  $C_{1-6}$  alkyl;

$R^4$  and  $R^5$  are independently selected from H,  $C_{1-6}$  alkyl or  
 20  $C_{1-6}$  alkyloxy,

with the proviso that when  $R^1$  and  $R^2$  are unsubstituted, unbranched  $C_{1-3}$  alkyl,  $R^3$  may not be



wherein R' is H or C<sub>1-3</sub> alkyl and R'' is H or o-  
 5 trifluoromethyl, m-trifluoromethyl or m-methoxy (see  
 4,281,000).

[9] The present invention also relates to a compound  
 according to group [8] wherein R<sup>3</sup> is substituted with 2-4  
 10 substituents.

[10] The present invention also relates to a compound  
 according to group [8] or [9] wherein R<sup>2</sup> is substituted  
 with 1-4 substituents.

15

[11] The present invention also relates to a compound  
 according to groups [8]-[10] having the formulae shown in  
 Table 1.

20 [12] The present invention also relates to a method of  
 antagonizing a CRF-1 receptor in mammals including humans  
 wherein binding to the receptor causes and ultimately  
 results in the treatment of affective disorder, anxiety,  
 depression, headache, irritable bowel syndrome, post-  
 25 traumatic stress disorder, supranuclear palsy, immune  
 suppression, Alzheimer's disease, gastrointestinal  
 diseases, anorexia nervosa or other feeding disorder,  
 drug addiction, drug or alcohol withdrawal symptoms,



inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy,  
 5 stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a  
 10 therapeutically effective amount of a compound of Formula (I) wherein

$R^1$  is selected from the group consisting of

- $C_{1-6}$  alkyl,
- 15  $C_{2-10}$  alkenyl,
- $C_{2-10}$  alkynyl,
- $C_{3-6}$  cycloalkyl,
- $C_{1-6}$  alkyloxy,
- $C_{1-6}$  alkylS(O)<sub>n</sub>,
- 20  $-NR^{1a}R^{1b}$  wherein  $R^{1a}$  and  $R^{1b}$  are independently selected from  
           H,  $C_{1-4}$  alkyl,  $-C(O)C_{1-4}$ alkyl,  
            $-C(O)NR^{1a}R^{1b}$ ,  
            $-O-C(O)C_{1-4}$ alkyl,
- 25  $-XR^{1c}$  wherein  $R^{1c}$  is selected from H or  $-C_{1-4}$  alkylaryl;  
           X is selected from O or S(O)<sub>n</sub>,

wherein  $R^1$  is substituted with 0-6 substituents selected from halogen,  $C_{1-4}$  alkyl,  $C_{1-6}$  alkyloxy,  $C_{1-4}$  haloalkyl, -  
 30  $NR^{1a}R^{1b}$ ,  $-XR^{1c}$ ;

$R^2$  is selected from the group consisting of  
 $C_{1-10}$  alkyl,

- C<sub>2-10</sub> alkenyl,
- C<sub>2-10</sub> alkynyl,
- C<sub>3-8</sub> cycloalkyl,
- C<sub>3-6</sub> cycloalkyl C<sub>1-6</sub> alkyl,
- 5 C<sub>1-10</sub> alkyloxy,
- C<sub>1-10</sub> alkyloxyC<sub>1-10</sub> alkyl,
- C<sub>1-4</sub> alkoxy C<sub>1-4</sub> alkyl,
- SO<sub>2</sub>-C<sub>1-10</sub>alkyl
- SO<sub>2</sub>R<sup>2a</sup> wherein R<sup>2a</sup> is aryl,
- 10 -SO<sub>2</sub>R<sup>2b</sup> wherein R<sup>2b</sup> is heteroaryl,
- NR<sup>2c</sup>R<sup>2d</sup> wherein R<sup>2c</sup> and R<sup>2d</sup> are independently selected from  
H, C<sub>1-8</sub> alkyl, C<sub>3-8</sub> cycloalkyl, C<sub>1-6</sub> alkyloxyC<sub>1-6</sub> alkyl,  
-C(O)C<sub>1-4</sub>alkyl or R<sup>2c</sup> and R<sup>2d</sup> may join to form a  
heterocyclic ring having 0-3 heteroatoms selected  
15 from O, N or S,
- halogen,
- CN,
- C(O)NR<sup>2c</sup>R<sup>2d</sup>,
- 20 -C(O)R wherein R is C<sub>1-6</sub> alkyl,
- C(O)OC<sub>1-4</sub> alkyl,
- C(O)O(CH<sub>2</sub>)<sub>2</sub>OR wherein R is C<sub>1-3</sub> alkyl,
- C(O)O(CH<sub>2</sub>)<sub>2</sub>-NHR wherein R is C<sub>1-3</sub> alkyl,
- C(O)O(CH<sub>2</sub>)<sub>2</sub>-NR<sup>2</sup>,
- 25 -C(O)OH,
- C(O)H,
- C(O)Ph,
- C(O)R' wherein R' is aryl, heteroaryl or carboalkoxy;
- 30
- n is 0, 1 or 2;

R<sup>2</sup> is substituted with 0-3 substituents independently

41

selected from R', R'', R''' wherein R', R'' and R''' are independently selected from C<sub>1-6</sub> alkyl, C<sub>3-7</sub> cycloalkyl, hydroxyC<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkyloxyC<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>1-6</sub> alkyloxy, hydroxy, or

5

R<sup>2</sup> is substituted with 0-3 substituents independently selected from

halogen,

-CN,

10 -S(O)<sub>n</sub>R<sup>2e</sup> wherein R<sup>2e</sup> is selected from C<sub>1-4</sub> alkyl, C<sub>1-4</sub> haloalkyl, C<sub>1-4</sub> alkyloxy C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl;

-COR<sup>2f</sup> wherein R<sup>2f</sup> is selected from H, C<sub>1-4</sub> alkyl, C<sub>1-4</sub>

haloalkyl, C<sub>1-4</sub> alkyloxy C<sub>1-4</sub> alkyl, C<sub>3-6</sub>

15 cycloalkyl, and C<sub>3-6</sub> cycloalkylC<sub>1-4</sub> alkyl;

-CO<sub>2</sub>R<sup>2f</sup>,

-NR<sup>2g</sup>COR<sup>2f</sup> wherein R<sup>2g</sup> is selected from H, C<sub>1-6</sub> alkyl, C<sub>3-7</sub> c-alkyl, C<sub>3-6</sub> cycloalkyl C<sub>1-6</sub> alkyl;

-N(COR<sup>2f</sup>)<sub>2</sub>,

20 -NR<sup>2g</sup>CONR<sup>2f</sup>R<sup>2h</sup>, wherein R<sup>2h</sup> is selected from H, C<sub>1-6</sub> alkyl, C<sub>1-4</sub> haloalkyl, C<sub>1-4</sub> alkoxy C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl and C<sub>3-6</sub> cycloalkylC<sub>1-6</sub> alkyl;

-NR<sup>2g</sup>CO<sub>2</sub>R<sup>2e</sup>,

25 -CONR<sup>2g</sup>R<sup>2h</sup>,

1-morpholinyl,

1-piperidinyl,

1-piperazinyl,

and

30 C<sub>3-8</sub> cycloalkyl wherein 0-1 carbon atoms in the C<sub>4-8</sub>

cycloalkyl is replaced by a group selected from

-O-, -S(O)<sub>n</sub>-, -NR<sup>2g</sup>-, -NCO<sub>2</sub>R<sup>2e</sup>, -NCOR<sup>2e</sup>,

and -NSO<sub>2</sub>R<sup>2e</sup>; and wherein N<sub>4</sub> in

42

1-piperazinyl is substituted with 0-1 substituents selected from  $R^{2g}$ ,  $CO_2R^{2e}$ ,  $COR^{2e}$  and  $SO_2R^{2e}$ ; or

- 5 the group  $R^{2i}$ ,  $R^{2j}$ ,  $R^{2k}$ ,  $C_{1-6}$  alkyl,  $C_{2-8}$  alkenyl,  $C_{2-8}$  alkynyl, Br, Cl, F, I,  $C_{1-4}$  haloalkyl,  $-OR^{2g}$ ,  $-NR^{2g}R^{2h}$ ,  $-C_{1-6}$  alkyl $OR^{2g}$ , and  $C_{3-8}$  cycloalkyl which is substituted with 0-1  $R^{2i}$  and in which 0-1 carbons of  $C_{4-8}$  cycloalkyl is replaced by -O-, wherein
- 10  $R^{2i}$  is selected from aryl wherein aryl includes phenyl, naphthyl, indanyl and indenyl, each  $R^{2i}$  being substituted with 0-1  $OR^{2m}$  and 0-5 substituents independently selected from the group  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl, Br, Cl, F, I,  $C_{1-4}$  haloalkyl, -CN, nitro, -SH,  $-S(O)_nR^{2n}$ ,  $-COR^{2m}$ ,  $-OC(O)R^{2n}$ ,  $-NR^{2g}COR^{2m}$ , -  
 $N(COR^{2m})_2$ ,  $-NR^{2g}CONR^{2o}R^{2p}$ ,  $-NR^{2g}CO_2R^{2n}$ ,  $-NR^{2o}R^{2p}$  and  $-CONR^{2o}R^{2p}$ ;
- $R^{2j}$  is selected from heteroaryl wherein heteroaryl
- 20 includes pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, 2,3-dihydrobenzothienyl-s-oxide, 2,3-dihydro-benzothienyl-S-dioxide, indolinyl, benzoxazolin-2-onyl, benzodioxolanyl and benzodioxane, each heteroaryl being substituted on 0-4 carbon atoms with a substituent independently selected
- 25 from the group  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl, Br, Cl, F, I,  $C_{1-4}$  haloalkyl, -CN, nitro,  $OR^{2m}$ , -SH,  $-S(O)_nR^{2h}$ ,  $-COR^{2m}$ , -  
 $OC(O)R^{2h}$ ,  $-NR^{2g}COR^{2m}$ ,  $-N(COR^{2m})_2$ ,  $-NR^{2g}CONR^{2o}R^{2p}$ ,  $-NR^{2g}CO_2R^{2h}$ , -  
 $NR^{2o}R^{2p}$  and  $-CONR^{2o}R^{2p}$  and each heteroaryl being substituted
- 30

on any nitrogen atom with 0-1 substituents selected from the group  $R^{2g}$ ,  $CO_2R^{2e}$ ,  $COR^{2e}$  and  $SO_2R^{2e}$ ;

$R^{2k}$  is heterocyclyl which is a saturated or partially saturated heteroaryl as defined for  $R^{2j}$ , each heterocyclyl being substituted on 0-4 carbon atoms with a substituent independently selected from the group  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl, Br, Cl, F, I,  $C_{1-4}$  haloalkyl, -CN, nitro,  $-OR^{2m}$ , -SH,  $-S(O)_nR^{2h}$ ,  $-COR^{2m}$ ,  $-OC(O)R^{2h}$ ,  $-NR^{2g}COR^{2m}$ ,  $-N(COR^{2m})_2$ ,  $-NR^{2g}CONR^{2o}R^{2p}$ ,  $NR^{2g}CO_2R^{2h}$ ,  $-NR^{2o}R^{2p}$  and  $-CONR^{2o}R^{2p}$  and each heterocyclyl being substituted on any nitrogen atom with 0-1 substituents selected from the group  $R^{2f}$ ,  $CO_2R^{2e}$ ,  $COR^{2e}$  and  $SO_2R^{2e}$ ;

wherein

$R^{21}$  is H,  $C_{1-4}$  alkyl,  $C_{3-6}$  cycloalkyl- $C_{1-4}$  alkyl and  $C_{3-6}$  cycloalkyl;

$R^{2m}$  is H,  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl  $C_{1-6}$  alkyl,  $C_{1-2}$  alkyloxy  $C_{1-2}$  alkyl,  $C_{1-4}$  haloalkyl,  $R^{2q}S(O)_n-C_{1-4}$  alkyl and  $R^{2r}R^{2s}N-C_{2-4}$  alkyl;

$R^{2n}$  is H,  $C_{1-6}$  alkyl,  $C_{3-10}$  cycloalkyl,  $C_{3-6}$  cycloalkyl- $C_{1-6}$  alkyl,  $C_{1-2}$  alkyloxy  $C_{1-2}$  alkyl, and  $C_{1-4}$  haloalkyl;

$R^{2o}$  and  $R^{2p}$  are independently selected at each occurrence from H,  $C_{1-6}$  alkyl,  $C_{3-10}$  cycloalkyl,  $C_{3-6}$  cycloalkyl  $C_{1-6}$  alkyl and  $C_{1-4}$  haloalkyl;

$R^{2q}$  is selected from  $C_{1-6}$  alkyl,  $C_{1-4}$  haloalkyl,  $C_{1-4}$  alkoxy- $C_{1-4}$  alkyl,  $C_{3-6}$  cycloalkyl,  $C_{3-6}$  cycloalkyl- $C_{1-6}$  alkyl, aryl, aryl( $C_{1-4}$  alkyl), heteroaryl and heteroaryl ( $C_{1-4}$  alkyl)-

44

and benzyl, each benzyl being substituted on the aryl moiety with 0-1 substituents selected from the group  $C_{1-4}$  alkyl, Br, Cl, F, I,  $C_{1-4}$  haloalkyl, nitro,  $C_{1-4}$  alkoxy  $C_{1-4}$  haloalkoxy, and dimethylamino;

5

$R^{2r}R^{2s}$  taken together with the N form 1-pyrrolidinyl, 1-morpholinyl, 1-piperidinyl or 1-piperazinyl wherein  $N_4$  in 1-piperiazinyl is substituted with 0-1 substituents selected from the group  $R^{2t}$ ,  $CO_2R^{2q}$ ,  $COR^{2q}$  and  $SO_2R^{2q}$ ;

10

$R^{2t}$  is selected from H,  $C_{1-4}$  alkyl,  $C_{1-4}$  haloalkyl,  $C_{1-4}$  alkoxy  $C_{1-4}$  alkyl,  $C_{3-6}$  cycloalkyl,  $C_{3-6}$  cycloalkyl -  $C_{1-6}$  alkyl, aryl, aryl ( $C_{1-4}$  alkyl)-, heteroaryl and heteroaryl ( $C_{1-4}$  alkyl);

15

$R^3$  is selected from an aryl or heteroaryl group attached through an unsaturated carbon atom;

aryl is selected from phenyl, naphthyl, indanyl and indenyl, each aryl being substituted with 0-5 substituents independently selected at each occurrence from  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl, methylenedioxy,  $C_{1-4}$  alkyloxy- $C_{1-4}$  alkyloxy,  $-OR^{2m}$ , Br, Cl, F, I,  $C_{1-4}$  haloalkyl, -CN,  $-NO_2$ , -SH,  $-S(O)_nR^{2n}$ ,  $-COR^{2m}$ ,  $-CO_2R^{2m}$ ,  $-OC(O)R^{2n}$ , -  
 25  $NR^{2q}COR^{2m}$ ,  $-N(COR^{2m})_2$ ,  $-NR^{2q}CONR^{2o}R^{2p}$ ,  $-NR^{2q}CO_2R^{2h}$ ,  $-NR^{2o}R^{2p}$  and  $CONR^{2o}R^{2p}$  and up to 1 phenyl, each phenyl substituent being substituted with 0-4 substituents selected from the group  $C_{1-3}$  alkyl,  $C_{1-3}$  alkoxy, Br, Cl, F, I, -CN, dimethylamino,  $CF_3$ ,  $C_2F_5$ ,  $OCF_3$ ,  $SO_2Me$  and acetyl;

30

heteroaryl is selected from the group pyridyl, pyrimidyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl,

- 45
- benzofuranyl, benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzo-furanyl, 2,3-dihydrobenzothienyl, 2,3-dihydro-benzothienyl-S-oxide, 2,3-dihydrobenzothienyl-s-dioxide, indolinyl, benzoxazolin-2-on-yl, benzodioxolanyl and benzodioxane, each heteroaryl being substituted at 0-4 carbon atoms with a substituent independently selected at each occurrence from the group  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl, Br, F, I,  $C_{1-4}$  haloalkyl, -CN,  $NR^{2g}R^{2h}$ , nitro,  $-OR^{2m}$ , -SH, -S(O) $R^{2n}$ ,  $COR^{2m}$ ,  $-CO_2R^{2m}$ ,  $-OC(O)R^{2n}$ ,  $-NR^{2g}COR^{2m}$ ,  $-N(COR^{2m})_2$ ,  $-NR^{2g}CONR^{2o}R^{2p}$  and each heteroaryl being substituted at any nitrogen atom with 0-1 substituents selected from the group  $R^{2g}$ ,  $CO_2R^{3a}$ ,  $COR^{3a}$  and  $SO_2R^{3a}$  wherein,
- 15  $R^{3a}$  is selected from the group  $C_{1-6}$  alkyl,  $C_{1-4}$  cycloalkyl- $C_{1-6}$  alkyl and benzyl, each benzyl being substituted on the aryl moiety with 0-1 substituents selected from the group  $C_{1-4}$  alkyl, Br, Cl, F, I,  $C_{1-4}$  haloalkyl, nitro,  $C_{1-4}$  alkoxy,  $C_{1-4}$  haloalkoxy, and dimethylamino;
- 20  $R^4$  and  $R^5$  are independently selected at each occurrence from H, Br, Cl, F, I, -CN,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{3-8}$  cycloalkyl,  $C_{1-6}$  alkyloxy,  $C_{1-6}$  alkylthio,  $C_{1-6}$  alkylsulfinyl,  $C_{1-6}$  alkylsulfonyl, amino,  $C_{1-4}$  alkylamino, (C<sub>1-4</sub> alkyl)<sub>2</sub> amino and phenyl, each phenyl is substituted
- 25 with 0-3 groups selected from the group consisting of  $C_{1-7}$  alkyl,  $C_{3-8}$  cycloalkyl, Br, Cl, F, I, -C(O)H,  $C_{1-4}$  haloalkyl, nitro,  $C_{1-4}$  alkoxy,  $C_{1-4}$  haloalkoxy,  $C_{1-4}$  alkylthio,  $C_{1-4}$  alkylsulfinyl,  $C_{1-4}$  alkylsulfonyl,  $C_{1-6}$  alkylamino and (C<sub>1-4</sub> alkyl)<sub>2</sub> amino and wherein  $R^4$  and  $R^5$
- 30 non-phenyl groups may be substituted with 0-5 substituents selected from OH, halogen, -C(O)H,  $-OC_{1-6}$ -alkyl and  $C_{1-6}$  haloalkyl,  $C_{1-6}$  alkyl,  $C_{3-7}$  c-alkyl,  $C_{1-6}$

alkyl(OH)<sub>n</sub>CO<sub>2</sub>R wherein R is H or C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkyl(OH)<sub>n</sub>, wherein n is 0-3 or R<sup>4</sup> and R<sup>5</sup> may join together to form a C<sub>3-6</sub> alkylene chain.

5 [13] The present invention also relates to a method as described directly above in group [12] wherein

R<sup>1</sup> is selected from C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkylthio, -XR<sup>1c</sup> wherein R<sup>1</sup> is substituted with 0-6 substituents selected from halogen, C<sub>1-4</sub> alkyl or C<sub>1-4</sub> haloalkyl;

R<sup>2</sup> is selected from substituted-C<sub>1-10</sub> alkyl, branched C<sub>3-10</sub> alkyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, C<sub>3-6</sub> cycloalkyl C<sub>1-6</sub> alkyl, -NR<sup>2c</sup>R<sup>2d</sup> wherein, in the case of substituted-C<sub>1-10</sub> alkyl, 1-3 substituents are

15 independently selected from the group R<sup>2i</sup>, R<sup>2j</sup>, R<sup>2k</sup>, C<sub>1-6</sub> alkyl, C<sub>2-8</sub> alkenyl, C<sub>2-8</sub> alkynyl, Br, Cl, F, I, C<sub>1-4</sub> haloalkyl, -OR<sup>2g</sup>, -NR<sup>2g</sup>R<sup>2h</sup>, -C<sub>1-6</sub> alkylOR<sup>2g</sup>, and C<sub>3-8</sub> cycloalkyl which is substituted with 0-1 R<sup>2i</sup> and in which 0-1 carbons of C<sub>4-8</sub> cycloalkyl is replaced by -O- and wherein the R<sup>2</sup>

20 groups, other than substituted-C<sub>1-10</sub> alkyl, are substituted with 0-3 substituents independently selected from the group R<sup>2i</sup>, R<sup>2j</sup>, R<sup>2k</sup>, C<sub>1-6</sub> alkyl, C<sub>2-8</sub> alkenyl, C<sub>2-8</sub> alkynyl, Br, Cl, F, I, C<sub>1-4</sub> haloalkyl, -OR<sup>2g</sup>, -NR<sup>2g</sup>R<sup>2h</sup>, -C<sub>1-6</sub> alkylOR<sup>2g</sup>, and C<sub>3-8</sub> cycloalkyl which is substituted with 0-1 R<sup>2i</sup> and in

25 which 0-1 carbons of C<sub>4-8</sub> cycloalkyl is replaced by -O-.

[14] The present invention also relates to a method described directly above in [12] or [13] wherein R<sup>3</sup> is selected from an aryl group selected from phenyl or

30 substituted versions thereof or a heteroaryl group selected from pyridyl or substituted versions thereof.



[15] The present invention relates to a method described directly above in groups [12]-[14] wherein R<sup>3</sup> is substituted with 0-4 substituents independently selected from halogen, C<sub>1-4</sub> alkyloxy, C<sub>1-6</sub> alkyl or NR'R'' wherein R' and R'' are independently selected from H or C<sub>1-6</sub> alkyl.

[16] The present invention preferably relates to a method as described directly above in groups [12]-[15] wherein R<sup>3</sup> is selected from 2,4-dichlorophenyl, 2-chloro-4-methoxyphenyl, 2,4,6-trimethylphenyl, 2,4,6-trimethoxyphenyl, 2-dimethylamino-4-methyl-pyridin-5-yl, 2,4-dichloro-5-fluorophenyl, 2-chloro-4-methoxy-5-fluorophenyl, 2-chloro-4,5-dimethoxyphenyl or 2-chloro-4,5-dimethoxyphenyl.

15

[17] The present invention also preferably relates to a method as described in groups [13]-[15] wherein R<sup>2</sup> is selected from C<sub>1</sub> alkyl of the formula -CR'R''R''' wherein R', R'' and R''' are independently selected from H, C<sub>1-6</sub> alkyl, C<sub>3-7</sub> cycloalkyl, hydroxyc<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkyloxyC<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>1-6</sub> alkyloxy, hydroxy, with the proviso that each of R', R'' and R''' cannot be H;

or R<sup>2</sup> is selected from NR'R'' wherein R' and R'' are independently selected from H or C<sub>1-6</sub> alkyl.

[18] The present invention preferably relates to a method according to groups [13]-[17] wherein R<sup>1</sup> is selected from an aryl or heteroaryl group attached through an unsaturated carbon atom wherein, aryl is phenyl, each phenyl being substituted with 0-5 substituents independently selected at each occurrence from C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, methylenedioxy, C<sub>1-4</sub>

30

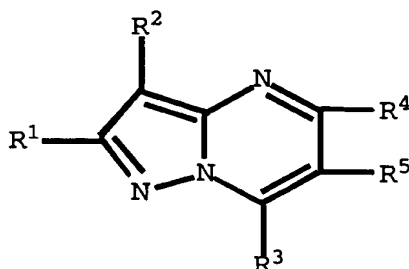
48

alkyloxy-C<sub>1-4</sub>, alkyloxy, -OR<sup>2m</sup>, Br, Cl, F, I, C<sub>1-4</sub> haloalkyl, -CN, -NO<sub>2</sub>, -SH, -S(O)<sub>n</sub>R<sup>2n</sup>, -COR<sup>2m</sup>, -CO<sub>2</sub>R<sup>2m</sup>, -OC(O)R<sup>2n</sup>, -NR<sup>2g</sup>COR<sup>2m</sup>, -N(COR<sup>2m</sup>)<sub>2</sub>, -NR<sup>2g</sup>CONR<sup>2o</sup>R<sup>2p</sup>, -NR<sup>2g</sup>CO<sub>2</sub>R<sup>2h</sup>, -NR<sup>2o</sup>R<sup>2p</sup> and CONR<sup>2o</sup>R<sup>2p</sup> and up to 1 phenyl, each phenyl substituent being substituted with 0-4 substituents selected from the group C<sub>1-3</sub>, alkyl, C<sub>1-3</sub>, alkoxy, Br, Cl, F, I, -CN, dimethylamino, CF<sub>3</sub>, C<sub>2</sub>F<sub>5</sub>, OCF<sub>3</sub>, SO<sub>2</sub>Me and acetyl and wherein, heteroaryl is selected at each occurrence from pyridyl, each pyridyl being substituted at 0-4 carbon atoms with a substituent independently selected at each occurrence from the group C<sub>1-6</sub>, alkyl, C<sub>3-6</sub> cycloalkyl, Br, F, I, C<sub>1-4</sub> haloalkyl, -CN, nitro, -OR<sup>2m</sup>, -SH, -S(O)<sub>n</sub>R<sup>2n</sup>, COR<sup>2m</sup>, -CO<sub>2</sub>R<sup>2m</sup>, -OC(O)R<sup>2n</sup>, -NR<sup>2g</sup>COR<sup>2m</sup>, -N(COR<sup>2m</sup>)<sub>2</sub>, -NR<sup>2g</sup>CONR<sup>2o</sup>R<sup>2p</sup> and each pyridyl being substituted at any nitrogen atom with 0-1 substituents selected from the group R<sup>2g</sup>, CO<sub>2</sub>R<sup>3a</sup>, COR<sup>3a</sup> and SO<sub>2</sub>R<sup>3a</sup>.

[19] The present invention preferably relates to a method of antagonizing a CRF-1 receptor in mammals including humans wherein binding to the receptor causes and ultimately results in the treatment of affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders

49

induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of formula (I)



(I)

5

or a pharmaceutically acceptable salt, stereoisomer or prodrug thereof, wherein

R<sup>1</sup> is selected from C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkyloxy, -SH or OH;

10

R<sup>2</sup> is selected from C<sub>1-4</sub> alkyl which is unsubstituted or substituted with 1-4 substituents selected from C<sub>1-6</sub> alkyl, C<sub>3-8</sub> cycloalkyl, C<sub>1-6</sub> alkylOR<sup>2g</sup>, C<sub>2-6</sub> alkenyl or OR<sup>2g</sup> wherein R<sup>2g</sup> is H or C<sub>1-6</sub> alkyl;

15

R<sup>3</sup> is selected from an aryl or heteroaryl group bonded through an unsaturated carbon atom that is unsubstituted or substituted with 1-4 substituents selected from Cl, F, I, Br, -OH, CF<sub>3</sub>, S(O)<sub>n</sub>C<sub>1-6</sub> alkyl, -OC<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkyl or NR<sup>2g</sup>R<sup>2h</sup> wherein R<sup>2g</sup> and R<sup>2h</sup> are independently selected from H or C<sub>1-6</sub> alkyl;

20

R<sup>4</sup> and R<sup>5</sup> are independently selected from H, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkyloxy.

25

50

[20] The present invention also relates to a method according to group [19] wherein  $R^3$  is substituted with 2-4 substituents.

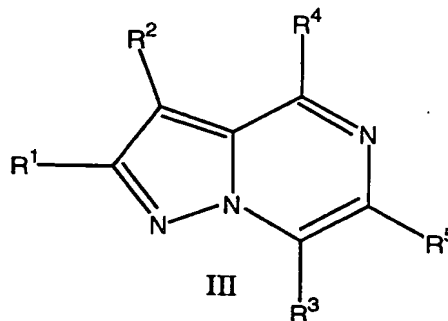
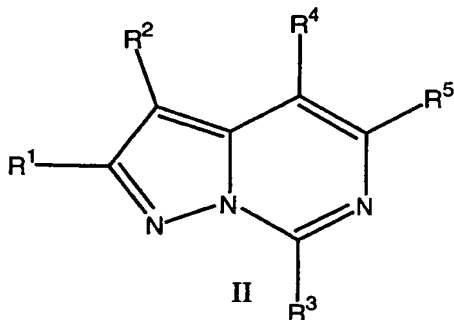
5 [21] The present invention also relates to a method according to group [19]-[20] wherein  $R^2$  is substituted with 1-4 substituents.

[22] The present invention also relates to a method  
10 according to group [19]-[21] using the formulae shown in Table 1.

[23] The present invention also provides pharmaceutical compositions comprising compounds of Formula (1) with  
15 the variables as recited above in group [1] and [1'] with the proviso that the compounds excluded in proviso (d) in group [1] are included herein and a pharmaceutically acceptable carrier.

20 [24] The preferred pharmaceutical compositions include those compounds as shown in groups [1'] and [2]-[11] along with a pharmaceutically acceptable carrier.

[25] The present invention also relates to a compound  
25 of the formulae shown below having the variables recited above in groups [1'] and [1]-[24]:



except that the provisos listed in group I are not  
30 included for the compounds of formula II and III.

[26] The present invention further comprises a compound of formula II or III in combination with a pharmaceutically acceptable excipient to form a pharmaceutical composition.

[27] The present invention further relates to a method of treating CRF related disorders or conditions or use in therapy of compounds of formula II or III comprising administering a compound of formula II or III with the variables for  $R^1$ - $R^5$  as shown above in groups [1'] and [1]-[24] to a patient in need of treatment thereof.

Many compounds of this invention have one or more asymmetric centers or planes. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms are included in the present invention. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds, and all such stable isomers are contemplated in the present invention. The compounds may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. All chiral, (enantiomeric and diastereomeric) and racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated.

The term "alkyl", unless otherwise specified, includes both branched and straight-chain alkyl having the specified number of carbon atoms. "Alkenyl" includes hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl, propenyl, and the like. "Alkynyl" includes hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any

52

stable point along the chain, such as ethynyl, propynyl and the like. "Haloalkyl" is intended to include both branched and straight-chain alkyl having the specified number of carbon atoms, substituted with 1 or more  
5 halogen; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge; "cycloalkyl" is intended to include saturated ring groups, including mono-, bi- or poly-cyclic ring systems, such as cyclopropyl, cyclobutyl,  
10 cyclopentyl, cyclohexyl, and so forth. "Halo" or "halogen" includes fluoro, chloro, bromo, and iodo.

The term "substituted", as used herein, means that one or more hydrogen on the designated atom is replaced with a selection from the indicated group, provided  
15 that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

Combinations of substituents and/or variables are  
20 permissible only if such combinations result in stable compounds. By "stable compound" or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious  
25 therapeutic agent.

The term "pharmaceutically acceptable salts" includes acid or base salts of the compounds of formulas (I). Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or  
30 organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like.

Pharmaceutically acceptable salts of the compounds of the invention can be prepared by reacting the free  
35 acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl

53

acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

"Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug of formula (I) in vivo when such prodrug is administered to a mammalian subject. Prodrugs of the compounds of formula (I) are prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compounds. Prodrugs include compounds wherein hydroxy, amine, or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of formulas (I) and the like.

The term "therapeutically effective amount" of a compound of this invention means an amount effective to antagonize abnormal level of CRF or treat the symptoms of affective disorder, anxiety, depression, immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress in a host.

The term "registry reference" refers to computer search generated sources of known chemical structures as identified by specific structure herein.

Compounds prepared according to the synthetic schemes and examples include, without limitation, those compounds specifically set forth in Table 1, hereinbelow, as well as the following:

7-(2,4-dichloro-5-fluorophenyl)-2-ethyl-3-(2-pentyl)-  
pyrazolo[1,5-a]pyrimidine  
7-(2,4-dichlorophenyl)-2-ethyl-6-methyl-3-(2-pentyl)-  
pyrazolo[1,5-a]pyrimidine  
7-(2-chloro-4-methoxyphenyl)-2-ethyl-3-(2-  
pentyl)pyrazolo[1,5-a]pyrimidine  
2-ethyl-3-(2-pentyl)-7-(2,4,6-trimethylphenyl)-  
pyrazolo[1,5-a]pyrimidine  
2-ethyl-3-(2-pentyl)-7-(2,4,6-trimethoxyphenyl)-  
pyrazolo[1,5-a]pyrimidine  
7-(2,4-dichlorophenyl)-2-ethyl-3-(2-pentyl)pyrazolo[1,5-  
a]pyrimidine  
7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidine-3-  
carboxaldehyde  
7-(2,4-dichlorophenyl)-2-ethyl-3-(1-hydroxyethyl)-  
pyrazolo[1,5-a]pyrimidine  
7-(2,4-dichlorophenyl)-3-(1-ethoxyethyl)-2-ethyl-  
pyrazolo[1,5-a]pyrimidine  
7-(2,4-dichlorophenyl)-3-(1-ethoxyethyl)-2-  
ethylpyrazolo[1,5-a]pyrimidine  
2-ethyl-7-(2-methyl-4-methoxyphenyl)-3-(3-pentyl)-  
pyrazolo[1,5-a]pyrimidine  
2-ethyl-7-(2-methyl-4-methoxyphenyl)-3-(2-pentyl)-  
pyrazolo[1,5-a]pyrimidine  
7-(2,4-dimethylphenyl)-2-ethyl-3-(2-pentyl)-pyrazolo[1,5-  
a]pyrimidine  
7-(2,4-dichlorophenyl)-2-ethyl-5-methylthio-3-(2-pentyl)-  
pyrazolo[1,5-a]pyrimidine  
7-(2,4-dichlorophenyl)-2-ethyl-3-(6-methyl-5-hepten-2-yl)-  
pyrazolo[1,5-a]pyrimidine  
7-(2,4-dichlorophenyl)-2-ethyl-3-(1-hydroxy-4-pentyl)-  
pyrazolo[1,5-a]pyrimidine  
7-(4-difluoromethoxy-2-methyl)-2-ethyl-3-(3-



53

pentyl)pyrazolo[1,5-a]pyrimidine  
7-(4-difluoromethoxy-2-methyl)-2-ethyl-3-(2-pentyl)pyrazolo[1,5-a]pyrimidine  
7-(2-chloro-4-difluoromethoxyphenyl)-2-ethyl-3-(3-pentyl)pyrazolo[1,5-a]pyrimidine  
7-(2-chloro-4-difluoromethoxyphenyl)-2-ethyl-3-(2-pentyl)pyrazolo[1,5-a]pyrimidine  
7-(2,4-dimethylphenyl)-2-ethyl-3-(3-pentyl)pyrazolo[1,5-a]pyrimidine  
4-(7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidinyl)pentanoic acid  
4-(7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidinyl)-N-methylpentanamide  
3-(5-(benzoxazol-2-ylthio)-2-pentyl)-7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidine  
3-(5-(benzoxazolidinethione-3-yl)-2-pentyl)-7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidine  
7-(2,4-dichlorophenyl)-2-ethyl-3-(1-hydroxy-2-propyl)-pyrazolo[1,5-a]pyrimidine  
7-(2,4-dichlorophenyl)-3-(1-ethoxy-2-propyl)-2-ethylpyrazolo[1,5-a]pyrimidine  
3-(1-acetoxy-2-propyl)-7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidine  
3-(1-acetoxy-2-butyl)-7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidine  
7-(2,4-dichlorophenyl)-2-ethyl-3-(1-hydroxy-3-butyl)pyrazolo[1,5-a]pyrimidine  
7-(2,4-dichlorophenyl)-2-ethyl-3-(1-methoxy-3-butyl)pyrazolo[1,5-a]pyrimidine  
7-(2,4-dichlorophenyl)-2-ethyl-3-(3-heptyl)-pyrazolo[1,5-a]pyrimidine  
7-(2,4-dichlorophenyl)-2-ethyl-3-(3-heptyl)-6-methylpyrazolo[1,5-a]pyrimidine

56

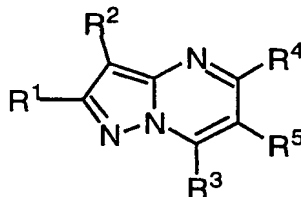
2-ethyl-3-(3-heptyl)-7-(2,4,6-trimethylphenyl)-  
pyrazolo[1,5-a]pyrimidine  
7-(2,4-dichlorophenyl)-2-ethyl-3-(3-pentyl)-pyrazolo[1,5-  
a]pyrimidine  
7-(2,4-dichlorophenyl)-2-ethyl-3-(3-pentyl)-6-methyl-  
pyrazolo[1,5-a]pyrimidine  
2-ethyl-3-(3-pentyl)-7-(2,4,6-trimethylphenyl)-  
pyrazolo[1,5-a]pyrimidine  
2-ethyl-3-(3-pentyl)-7-(2,4,6-trimethoxyphenyl)-  
pyrazolo[1,5-a]pyrimidine

### Synthesis

5           Compounds of formula (I) can be prepared by the  
following synthetic routes and schemes. Where a detailed  
description is not provided, it is assumed that those  
skilled in the art of organic synthesis will readily  
understand the meaning.

10           Synthesis of compounds of formula (I) may be  
prepared by the reaction shown in Scheme 1.

          The embodiment of this invention concerning  
15   compounds of Formula (I) with the structure



may be prepared according to the following methods:

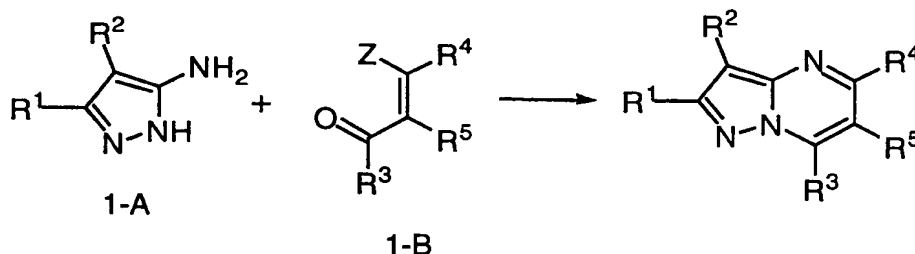
          The pyrazolo[1,5-a]pyrimidine ring system is best  
prepared by the condensation reaction of a 3-  
20   aminopyrazole (1-A, Scheme 1A) with a compound of formula

57

1-B. Here, Z is ethoxy or dimethylamino, and compound 1-B may be prepared by the reaction of a compound of formula  $R^3C(=O)CH_2R^6$  with a reagent of formula  $R^5C(Z)(OEt)_2$ . These types of reactions are normally done by heating the two compounds (as a 1:1 mixture) without solvent, and distilling off the volatile components after the reaction is complete. The reaction between 1-A and 1-B is conveniently performed in a solvent such as acetic acid with heating; the acetic acid acts as both solvent and catalyst for the condensation.

Preparation of the pyrazoles can begin with the acylation of a nitrile compound 1-C (Scheme 1B). Normally, a strong base, such as lithium diisopropylamide, is used to deprotonate the nitrile, and the resulting anionic intermediate is treated with a carboxylic ester  $R^1CO_2Et$  or

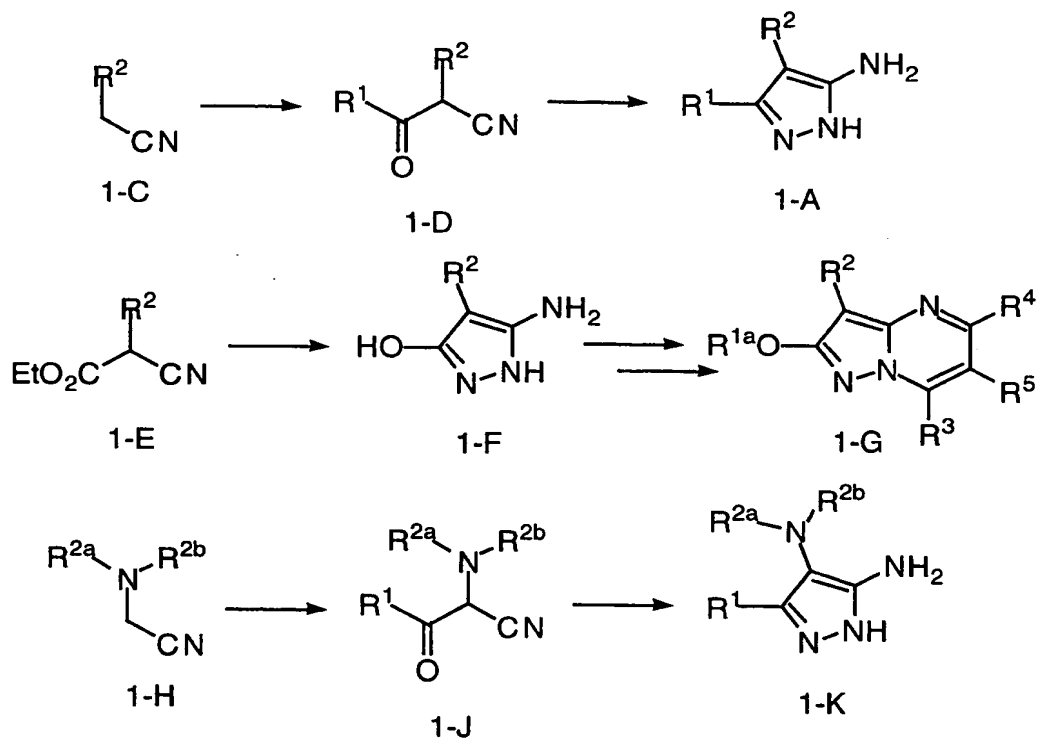
Scheme 1A



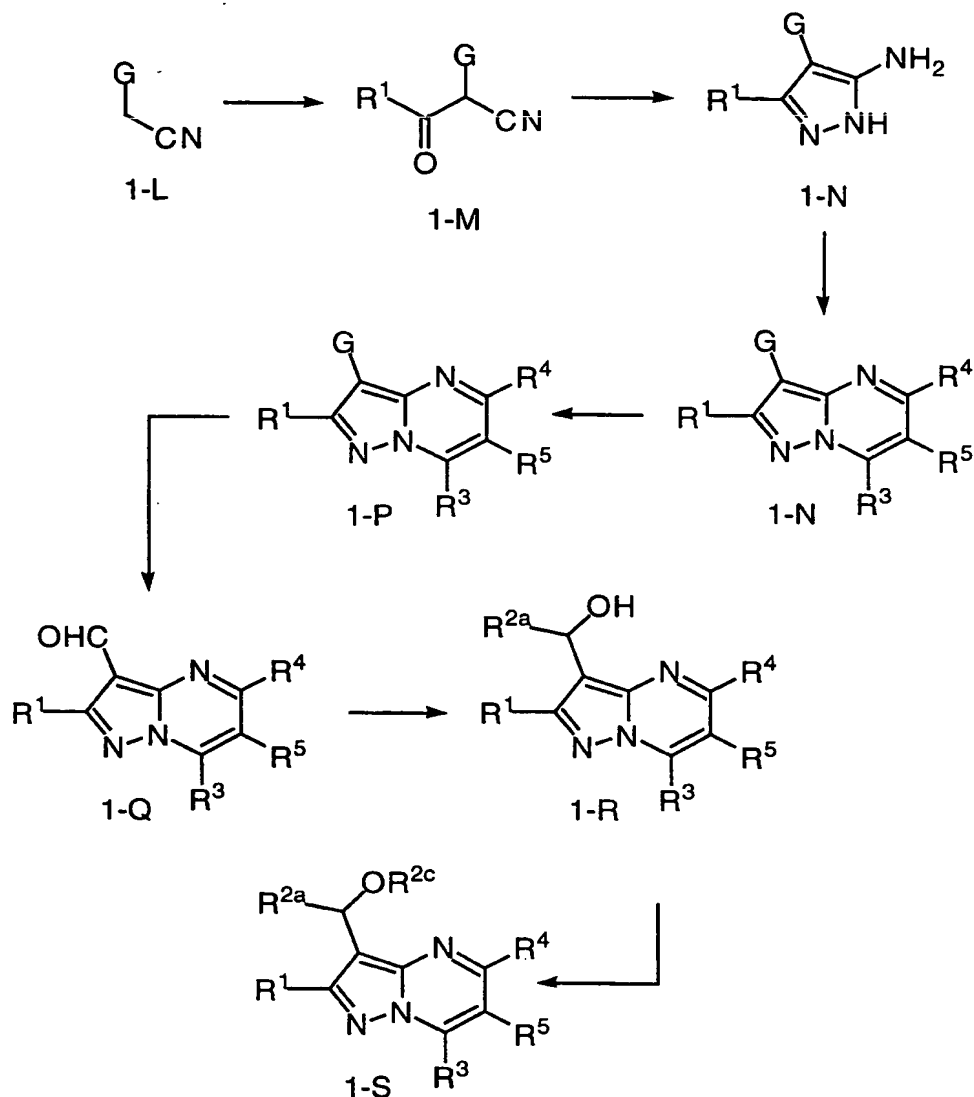
acid chloride  $R^1COCl$  to generate the ketonitrile 1-D. Condensation of this compound with hydrazine then gives the aminopyrazole. This reaction may be performed in refluxing alcoholic solvent with the optional presence of an acid catalyst, such as acetic acid. Heteroatomic versions of this route are possible. Aminopyrazoles with an  $R^1$  group wherein  $R^1 = R^{1a}O$  may be prepared by starting with cyanoacetic esters like 1-E, which react with hydrazine to afford 3-amino-5-hydroxypyrazole 1-F.

58

Cyclization with reagent 1-B and O-alkylation with a reagent  $R^{1a}X$ , wherein X is a halide or pseudohalide group, gives compound 1-G. Finally, strong base treatment of aminonitrile 1-H, usually in the presence of a solvent mixture such as THF/HMPA, followed by acylation and ring-forming, gives diamine 1-K.

Scheme 1B

57  
Scheme 1C



Scheme 1C shows one application of a variation involving a group G (carboalkoxy or CN) which can serve as a functional handle for various R<sup>2</sup> substitutions. Since G is activating, the acylation of 1-L to give 1-M may not require as strong a base as is used for the transformation of 1-C to 1-D; a reagent such as an orthoester may also be used. Subsequent ring condensations to 1-N and then to 1-P proceed as described earlier. Then, the group G is converted to the R<sup>2</sup> group of

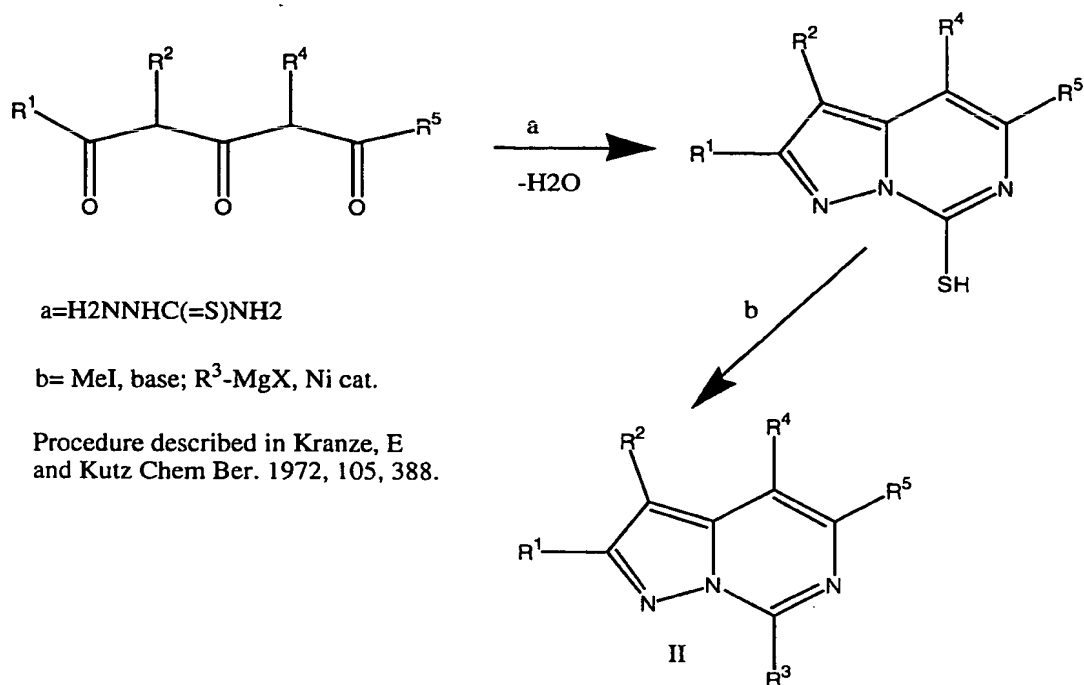
choice wherein  $R^2$  and substituted versions thereof is as defined in the claims and as above in the specification; the following method is one example. Use of a reducing agent such as diisobutylaluminum hydride in a solvent  
5 like toluene or dichloromethane at low temperatures can be used to obtain the aldehyde 1-Q. The aldehyde may be allowed to react with organometallic reagents such as the Grignard reagent  $R^{2a}MgBr$  to afford the alcohol 1-R. The hydroxy group may then be O-alkylated (typically using a  
10 reagent  $R^{2c}X$  and a base such as sodium hydride in a polar aprotic solvent such as DMF) to give the compound 1-S. Other such manipulations of the G group should be familiar to those skilled in the art of organic synthesis.

15 Similarly, the remaining variables in the starting materials described above such as  $R^1$  or  $R^3$  are determined based upon the desired target moiety. Thus, varying the ketone 1-B with respect to the aryl or heteroaryl group  $R^3$  permits synthesis of a compound of formula I having  $R^3$  as  
20 the desired heteroaryl or aryl group and substituted versions thereof as recited in the claims and above text and as further shown in the examples and table before the appended claims.

The synthesis of compounds of formula II or III may  
25 be accomplished by the general schemes shown below in Scheme 2 and in Scheme 3.

61

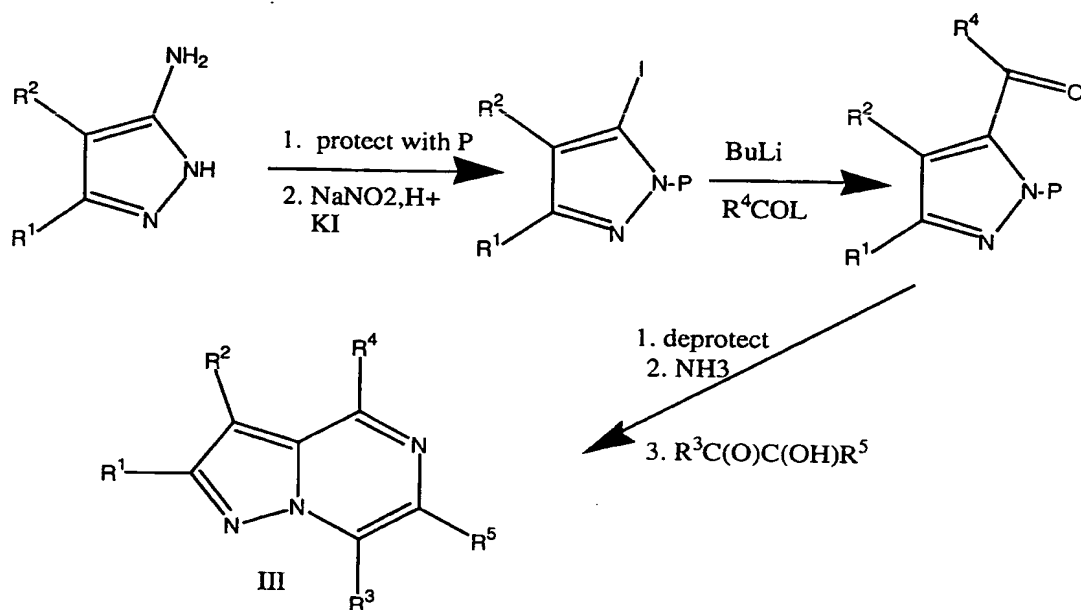
## SCHEME 2



The variables for  $\text{R}^1\text{-R}^5$  are selected from those variables as defined in any of the groups [1]-[24]. The compound of formula II is prepared by starting with the acyclic triketone intermediate shown above which is reacted with reagent a to form the bicyclic intermediate which is then treated with the grignard reagent b to form a compound of formula II.

62

SCHEME 3



The variables for  $\text{R}^1$ - $\text{R}^5$  in Scheme 3 are selected from those described in groups [1]-[24]. Compounds II and III  
 5 with the variables as defined above are useful as CRF antagonists.

10

### Utility

#### CRF-R1 Receptor Binding Assay for the Evaluation of Biological Activity

15

#### Radioligand binding experiments

Compounds of the invention were tested for in vitro activity as CRF receptor antagonists. The tests described below demonstrated that the examples tested had  $K_i$ s of 10,000 nM or less and are thus useful as CRF  
 20 receptor antagonists. Preferred antagonists have or will have a  $K_i$  of 1,000 nM or less. Radioligand binding experiments were performed with membranes from rat



frontal cortex to determine binding affinities ( $K_i$ 's) of test compounds for the rat CRH<sub>1</sub> receptor using a modified version of methods described earlier (see E.B. DeSouza, J. Neurosci, 7:88, 1987). Rat cortex was homogenized in  
5 tissue buffer (containing 50 mM HEPES, 10 mM MgCl<sub>2</sub>, 2 mM EGTA, and 1 µg/ml each of aprotonin, leupeptin, and pepstatin, pH 7.0 @ 23°C) using a Brinkman Polytron (PT-10, setting 6 for 10 sec). The homogenate was centrifuged at 48,000 X g for 12 min and the resulting pellet was  
10 washed by two sequential re-suspension and centrifugation steps. The final pellet was suspended to tissue buffer to a working concentration of 0.1 mg/ml protein. Protein determinations were made using the bicinchoninic acid (BCA) assay (Pierce, Rockford, IL) with bovine serum  
15 albumin as the standard.

All test compounds were prepared in assay buffer, which was identical to the tissue buffer except for the inclusion of 0.15 mM bacitracin and 0.1% w/v ovalbumin. Binding assay were conducted in disposable  
20 polypropylene 96-well plates (Costar Corp., Cambridge, MA) and initiated by the addition of 100 µl membrane homogenate (containing 40-60 µg protein) to 200 µl of assay buffer containing radioligands (150 pM, final concentration, [<sup>125</sup>I] tyr<sup>o</sup> ovine CRH; New England  
25 Nuclear, MA) and competing test compounds. Specific binding was determined in the presence of 10 µM α-helical CRH. Competition experiments were conducted using 12 concentrations of ligand (ranging from 1 X 10<sup>-11</sup> to 1 X 10<sup>-5</sup> M). The reactions mixtures were incubated  
30 to equilibrium for 2 hr at 23°C and terminated by rapid filtration using a cell harvester (Inotech Biosystems Inc., Lansing MI) over GFF glass-fibers (pre-soaked in 0.3 % v/v polyethyleneimine). Filters were rapidly washed 3X with 0.3 ml cold wash buffer (PBS, pH 7.0,  
35 containing 0.01% Triton X-100), dried, and counted in a gamma counter at 80% efficiency.

64

Binding affinities ( $K_i$ 's) of ligands for the CRH<sub>1</sub> receptor were calculated using the iterative nonlinear regression curve-fitting programs (LIGAND) of Munson and Rodbard (Anal. Biochem. 1980, 107, 220-239) or  
5 Prism (GraphPad Prism, San Diego, CA). Data were best-fit by the one-site/state competition equation.

#### Inhibition of CRF-Stimulated Adenylate Cyclase Activity

Inhibition of CRF-stimulated adenylate cyclase  
10 activity can be performed as described by G. Battaglia et al. Synapse 1:572 (1987). Briefly, assays are carried out at 37° C for 10 min in 200 ml of buffer containing 100 mM Tris-HCl (pH 7.4 at 37° C), 10 mM MgCl<sub>2</sub>, 0.4 mM EGTA, 0.1% BSA, 1 mM  
15 isobutylmethylxanthine (IBMX), 250 units/ml phosphocreatine kinase, 5 mM creatine phosphate, 100 mM guanosine 5'-triphosphate, 100 nM oCRF, antagonist peptides (concentration range 10<sup>-9</sup> to 10<sup>-6</sup>m) and 0.8 mg  
20 original wet weight tissue (approximately 40-60 mg protein). Reactions are initiated by the addition of 1 mM ATP/<sup>32</sup>P]ATP (approximately 2-4 mCi/tube) and terminated by the addition of 100 ml of 50 mM Tris-HCL, 45 mM ATP and 2% sodium dodecyl sulfate. In order to  
25 monitor the recovery of cAMP, 1 µl of [<sup>3</sup>H]cAMP (approximately 40,000 dpm) is added to each tube prior to separation. The separation of [<sup>32</sup>P]cAMP from [<sup>32</sup>P]ATP is performed by sequential elution over Dowex and alumina columns.

#### 30 In vivo Biological Assay

The in vivo activity of the compounds of the present invention can be assessed using any one of the biological assays available and accepted within the art. Illustrative of these tests include the Acoustic  
35 Startle Assay, the Stair Climbing Test, and the Chronic Administration Assay. These and other models useful for the testing of compounds of the present invention

65

have been outlined in C.W. Berridge and A.J. Dunn Brain Research Reviews 15:71 (1990).

5 Compounds may be tested in any species of rodent or small mammal.

Compounds of this invention have utility in the treatment of imbalances associated with abnormal levels of corticotropin releasing factor in patients suffering from depression, affective disorders, and/or anxiety.

10 Compounds of this invention can be administered to treat these abnormalities by means that produce contact of the active agent with the agent's site of action in the body of a mammal. The compounds can be administered by any conventional means available for use in  
15 conjunction with pharmaceuticals either as individual therapeutic agent or in combination of therapeutic agents. They can be administered alone, but will generally be administered with a pharmaceutical carrier selected on the basis of the chosen route of  
20 administration and standard pharmaceutical practice.

The dosage administered will vary depending on the use and known factors such as pharmacodynamic character of the particular agent, and its mode and route of administration; the recipient's age, weight, and  
25 health; nature and extent of symptoms; kind of concurrent treatment; frequency of treatment; and desired effect. For use in the treatment of said diseases or conditions, the compounds of this invention can be orally administered daily at a dosage of the  
30 active ingredient of 0.002 to 200 mg/kg of body weight. Ordinarily, a dose of 0.01 to 10 mg/kg in divided doses one to four times a day, or in sustained release formulation will be effective in obtaining the desired pharmacological effect.

35 Dosage forms (compositions) suitable for administration contain from about 1 mg to about 100 mg of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be

66

present in an amount of about 0.5 to 95% by weight based on the total weight of the composition.

The active ingredient can be administered orally is solid dosage forms, such as capsules, tablets and  
5 powders; or in liquid forms such as elixirs, syrups, and/or suspensions. The compounds of this invention can also be administered parenterally in sterile liquid dose formulations.

Gelatin capsules can be used to contain the active  
10 ingredient and a suitable carrier such as but not limited to lactose, starch, magnesium stearate, steric acid, or cellulose derivatives. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release  
15 products to provide for continuous release of medication over a period of time. Compressed tablets can be sugar-coated or film-coated to mask any unpleasant taste, or used to protect the active ingredients from the atmosphere, or to allow selective  
20 disintegration of the tablet in the gastrointestinal tract.

Liquid dose forms for oral administration can contain coloring or flavoring agents to increase patient acceptance.

25 In general, water, pharmaceutically acceptable oils, saline, aqueous dextrose (glucose), and related sugar solutions and glycols, such as propylene glycol or polyethylene glycol, are suitable carriers for parenteral solutions. Solutions for parenteral  
30 administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents, such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or in combination, are  
35 suitable stabilizing agents. Also used are citric acid and its salts, and EDTA. In addition, parenteral solutions can contain preservatives such as

benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences", A. Osol, a  
5 standard reference in the field.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

10

#### Capsules

A large number of units capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 mg of powdered active ingredient, 150 mg lactose, 50 mg cellulose, and 6 mg magnesium stearate.

15

#### Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean, cottonseed oil, or olive oil is prepared and injected by means of a positive  
20 displacement was pumped into gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules were washed and dried.

#### Tablets

25 A large number of tablets are prepared by conventional procedures so that the dosage unit was 100 mg active ingredient, 0.2 mg of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch, and 98.8  
30 mg lactose. Appropriate coatings may be applied to increase palatability or delayed adsorption.

The preferred indication and use of the compounds and compositions of the invention is in the treatment of depression or anxiety.

35

The compounds of this invention may also be used as reagents or standards in the biochemical study of neurological function, dysfunction, and disease.

68

The following examples are provided to describe the invention in further detail. These examples, which set forth the best mode presently contemplated for carrying out the invention, are intended to illustrate and not to limit the invention.

### Examples

The following specific synthetic example describes the procedures which, when applied to appropriately substituted substrates, may be employed in the synthesis of the compounds in Table 1.

#### Example 1

##### Preparation of 7-(2,4-dichlorophenyl)-2-ethyl-3-(3-pentyl)pyrazolo[1,5-a]pyrimidine

Part A. A mixture of 2-ethyl-1-bromobutane (10.0 mL, 71.4 mmol), potassium cyanide (14.0 g, 215 mmol) and aliquat 336 (10 drops) in 50 mL water was heated to reflux overnight with vigorous stirring. The mixture was cooled, and extracted with dichloromethane (2 x 50 mL). The extracts were combined, dried over magnesium sulfate, filtered and evaporated. The residual liquid was distilled bulb-to-bulb to afford pure product, 3-ethylpentanenitrile (5.50 g, 49.5 mmol, 69%). b.p. 40-45 °C (5 mm Hg). Spectral data: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 2.33 (2H, d, J = 5.8 Hz), 1.62-1.36 (5H, m), 0.92 (6H, t, J = 7.3 Hz). MS (H<sub>2</sub>O-GC/MS): m/e 112 (100).

Part B. A solution of diisopropylamine (7.50 mL, 57.2 mmol) in THF (100 mL) was cooled to -78 °C, and treated

with n-butyllithium (34.0 mL of a 1.6 M solution in hexane). The solution was warmed briefly to 0 °C, and then recooled to -78 °C. The nitrile compound from Part A was then added by syringe, and the solution was allowed to stir for 1 hour. Then, ethyl propionate (6.50 mL, 56.7 mmol) was added by syringe, and the resulting mixture was allowed to stir and warm to ambient temperature for 12 hours. It was poured into 200 mL of satd. aq.  $\text{NH}_4\text{Cl}$  solution, and this was extracted with ethyl acetate (2 x 200 mL). The extracts were combined, dried over magnesium sulfate, filtered and evaporated. The residual oil was separated by column chromatography (silica gel, 10:90 ethyl acetate-hexane) to afford the product, 4-cyano-5-ethyl-3-heptanone, as an oil 4.06 g, 24.3 mmol, 49%). TLC  $R_f$  0.47 (20:80 ethyl acetate-hexane). Spectral data:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  3.49 (1H, d,  $J$  = 4.4 Hz), 2.74 (2H, q,  $J$  = 7.3 Hz), 2.08-1.98 (1H, m), 1.70-1.58 (1H, m), 1.50-1.20 (3H, m), 1.12 (3H, t,  $J$  = 7.3 Hz), 0.95 (3H, t,  $J$  = 7.3 Hz), 0.91 (3H, t,  $J$  = 7.3 Hz). MS ( $\text{H}_2\text{O}$ -GC/MS):  $m/e$  167 (100).

Part C. A solution of the ketonitrile from Part B (4.06 g, 24.3 mmol), hydrazine hydrate (2.70 mL, 55.7 mmol) and acetic acid (5.00 mL, 83.7 mmol) in benzene (50 mL) was heated to reflux under a Dean-Stark trap with azeotropic distillation of water. After being heated for 12 hours, the mixture was cooled and poured into 100 mL 1 N aq.  $\text{NaHCO}_3$  solution. This was extracted with ethyl acetate (2 x 100 mL), and the extracts were washed in sequence with brine, combined, dried over sodium sulfate, filtered and evaporated to afford sufficiently-pure product, 3-amino-5-ethyl-4-(3-pentyl)pyrazole, as a viscous oil (2.48 g,

13.7 mmol, 56%). Spectral data:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  3.48 (2H, br), 2.54 (2H, q,  $J = 7.3$  Hz), 2.25-2.14 (1H, m), 1.71-1.49 (4H, m), 1.20 (3H, t,  $J = 7.3$  Hz), 0.83 (6H, t,  $J = 7.3$  Hz), 1H missing. MS ( $\text{NH}_3$ -CI): m/e 183 (12), 182 (100).

Part D. A mixture of 2,4-dichloroacetophenone (10.0 g, 52.9 mmol) and dimethylformamide diethyl acetal (10.0 mL, 58.3 mmol) was heated to reflux for 12 hours, then cooled and evaporated under high vacuum. The residual oil was separated by column chromatography (silica gel, 1:1 ethyl acetate-hexane) to afford the product, 1-(2,4-dichlorobenzoyl)-2-(N,N-dimethylamino)ethene, as a viscous oil (12.11 g, 49.6 mmol, 94%). TLC  $R_f$  0.05 (20:80 ethyl acetate-hexane). Spectral data:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.40 (1H, d,  $J = 2.2$  Hz), 7.38-7.23 (3H, m), 5.33 (1H, d,  $J = 12.4$  Hz), 3.11 (3H, br s), 2.89 (3H, br s). MS ( $\text{NH}_3$ -CI): m/e 249 (1), 248 (10), 247 (8), 246 (64), 245 (16), 244 (100).

Part E. A solution of the product of Part C (2.25 g, 1.38 mmol) and that of Part D (0.337 g, 1.38 mmol) in acetic acid (5 mL) was heated to reflux for 10 hours, then cooled, and poured into water. This was neutralized by the addition of solid sodium bicarbonate until the evolution of  $\text{CO}_2$  subsided. The resulting mixture was extracted with ethyl acetate (2 x 100 mL), and the extracts were washed with brine (100 mL), combined, dried over sodium sulfate, filtered and evaporated. The resulting mixture of regioisomeric products (ca. 5:1 estimated by TLC visualization) were separated by column chromatography (silica gel, 10:90 ethyl acetate-hexane) to afford the major regioisomer as the more TLC-mobile



71

product, which was the title compound. TLC R<sub>f</sub> 0.32 (10:90 ethyl acetate-hexane). Spectral data: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.38 (1H, d, J = 4.1 Hz), 7.58 (1H, d, J = 2.0 Hz), 7.55 (1H, d, J = 8.2 Hz), 7.41 (1H, dd, J = 8.2, 2.0 Hz), 6.65 (1H, d, J = 4.1 Hz), 2.79 (2H, q, J = 7.7 Hz), 2.78-2.68 (1H, m), 2.03-1.79 (4H, m), 1.25 (3H, t, J = 7.7 Hz), 0.83 (6H, t, J = 7.3 Hz). MS (NH<sub>3</sub>-CI): m/e 367 (2), 366 (11), 365 (15), 364 (65), 363 (25), 362 (100). Analysis calc'd for C<sub>19</sub>H<sub>21</sub>Cl<sub>2</sub>N<sub>3</sub>: C, 62.99; H, 5.84; N, 11.60; found: C, 62.97; H, 5.74; N, 11.49.

Examples 2-30 were prepared and/or may be prepared in an analogous fashion.

Example 31Preparation of 7-(2,4-dichlorophenyl)-3-(N,N-diethylamino)-2-ethylpyrazolo[1,5-a]pyrimidine

- 5 Part A. A solution of diisopropylamine (10.0 mL, 76.3 mmol) in THF (60 mL) was cooled to -78 °C, and treated with n-butyllithium (50.0 mL of a 1.6 M solution in hexane). The solution was warmed briefly to 0 °C, and then recooled to
- 10 -78 °C. To this was added first, N,N'-dimethylpropyleneurea as cosolvent (15 mL), then, diethylaminoacetone (10.0 mL, 74.1 mmol), and the solution was allowed to stir for 1 hour. Then, ethyl propionate (10.0 mL, 87.2 mmol) was added by syringe, and
- 15 the resulting mixture was allowed to stir and warm to ambient temperature for 12 hours. It was poured into 200 mL of satd. aq.  $\text{NH}_4\text{Cl}$  solution, and this was extracted with ethyl acetate (2 x 200 mL). The extracts were combined, dried over magnesium sulfate, filtered and
- 20 evaporated. The residual oil was separated by column chromatography (silica gel, 20:80 ethyl acetate-hexane) to afford the product, 2-(N,N-diethylamino)-3-oxopentanenitrile, as an oil (5.31 g, 31.6 mmol, 43%).
- 25 Part B. A solution of the ketonitrile from Part A, hydrazine hydrate (3.00 mL, 61.9 mol) and acetic acid (6.00 mL, 104 mmol) in benzene (100 mL) was heated to reflux under a Dean-Stark trap with azeotropic removal of water for a period of 14 hours. Excess hydrazine (2 mL)
- 30 and excess acetic acid (5 mL) were then added, and refluxing was allowed to continue for 20 hours. The solution was cooled and poured into 200 mL 1 N aq.  $\text{NaHCO}_3$  solution. This was extracted with ethyl acetate (2 x 200

- mL), and the extracts were washed in sequence with brine, combined, dried over sodium sulfate, filtered and evaporated. The residue was separated by column chromatography (silica gel, 30:70 ethyl acetate to remove unreacted starting material, then ethyl acetate) to afford the product, 3-amino-4-(N,N-diethylamino)-5-ethylpyrazole, as a viscous oil which darkens in air (750 mg, 4.41 mmol, 15%).
- 10 Part C. A solution of the diamine from Part B (300 mg, 1.76 mmol) and 1-(2,4-dichlorobenzoyl)-2-(N,N-dimethylamino)ethene (470 mg, 1.93 mmol) in acetic acid (5 mL) was heated to 100 °C for 10 hours, then cooled and poured into satd. aq. NaHCO<sub>3</sub> solution (100 mL). This mixture was extracted with ethyl acetate (2 x 100 mL), and the extracts were washed with brine, combined, dried over sodium sulfate, filtered and evaporated. The residual oil was separated by column chromatography (silica gel, 20:80 ethyl acetate-hexane) to afford the title product as a red oil (411 mg, 1.13 mmol, 64%).
- 20 Spectral data: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.38 (1H, d, J = 4.0 Hz), 7.58 (1H, d, J = 1.8 Hz), 7.56 (1H, d, J = 8.4 Hz), 7.42 (1H, dd, J = 8.4, 1.8 Hz), 6.65 (1H, d, J = 4.0 Hz), 3.27 (4H, q, J = 7.3 Hz), 2.80 (2H, q, J = 7.3 Hz), 1.26 (3H, t, J = 7.3 Hz), 1.00 (6H, t, J = 7.3 Hz). MS (NH<sub>3</sub>-CI): calculated for C<sub>18</sub>H<sub>21</sub>Cl<sub>2</sub>N<sub>4</sub>, 363.1143, measured 363.1146; m/e 367 (6), 366 (14), 365 (81), 364 (28), 363 (100).
- 30 Examples 32-45 were and/or may be prepared in an analogous manner.

74

Preparation of 7-(2,4-dichlorophenyl)-2-hydroxy-6-methyl-3-(3-pentyl)pyrazolo[1,5-a]pyrimidine (92) and 7-(2,4-dichlorophenyl)-2-methoxy-6-methyl-3-(3-pentyl)pyrazolo[1,5-a]pyrimidine (51)

5

Part A. A solution of triphenylphosphine (25.0 g, 95.3 mmol) in THF (200 mL) was cooled to -30 °C, and diethyl azodicarboxylate (15.0 mL, 95.2 mmol) was slowly added dropwise in conc. THF solution. After the addition was complete, the mixture was treated with a THF solution of 3-pentanol (10.0 mL, 90.6 mmol) and ethyl cyanoacetate (10.0 mL, 92.1 mmol). The resulting mixture was allowed to stir and warm to ambient temperature for 12 hours, then was evaporated. The residual oil was separated by column chromatography (10:90 ethyl acetate-hexane) to afford the product, ethyl 2-cyano-3-ethylpentanoate, as a viscous oil (3.41 g, 18.6 mmol, 21%). TLC R<sub>f</sub> 0.43 (20:80 ethyl acetate-hexane). Spectral data: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 4.27 (2H, q, J = 7.0 Hz), 3.61 (1H, d, J = 4.4 Hz), 2.04-1.93 (1H, m), 1.70-1.35 (4H, m), 1.33 (3H, t, J = 7.0 Hz), 0.97 (3H, t, J = 7.3 Hz), 0.94 (3H, t, J = 7.3 Hz). MS (H<sub>2</sub>O-GC/MS): m/e 185 (8), 184 (100).

Part B. A solution of the cyanoester from Part A and hydrazine hydrate (2.00 mL, 41.2 mmol) in ethanol (30 mL) was heated to reflux for 10 hours. The solution was cooled, and poured into water. This was extracted with ethyl acetate (2 x 100 mL), and the extracts were washed with brine, combined, dried over sodium sulfate, filtered and evaporated. The resulting oil was sufficiently pure product, 3-amino-5-hydroxy-4-(3-pentyl)pyrazole (1.29 g, 7.62 mmol, 41%).

75

- Part C. A solution of the pyrazole compound from Part B (478 mg, 2.82 mmol) and 2-(2,4-dichlorobenzoyl)-1-(N,N-dimethylamino)-1-propene (729 mg, 2.82 mmol) in acetic acid (10 mL) was heated to reflux for 10 hours. The solution was cooled and poured into water (100 mL). This was neutralized by the addition of solid NaHCO<sub>3</sub>, and the mixture was extracted with ethyl acetate (2 x 100 mL). The extracts were washed with brine, combined, dried over sodium sulfate, filtered and evaporated. The residue was separated by column chromatography (silica gel, 10:90 ethyl acetate-hexane) to give the compound of Example 92 as a solid (210 mg, 0.576 mmol, 20%). m.p. 227-228 °C. TLC R<sub>f</sub> 0.46 (20:80 ethyl acetate-hexane). Spectral data: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 10.53 (1H, br s), 8.27 (1H, s), 7.63 (1H, d, J = 2.2 Hz), 7.45 (1H, dd, J = 8.4, 2.2 Hz), 7.25 (1H, d, J = 8.4 Hz), 2.72-2.62 (1H, m), 2.02 (3H, s), 1.77-1.65 (4H, m), 0.82 (6H, t, J = 7.5 Hz). MS (ESI): m/e 366 (69), 364 (100).
- Part D. A solution of the compound of Example 92 (31 mg, 0.085 mmol) and Proton-Sponge™ (20 mg, 0.093 mmol) in acetonitrile (2 mL) was cooled to 0 °C, and treated with methyl methanetrifluorosulfonate (10 µL, 0.088 mmol). After stirring for 10 hours and warming to ambient temperature, the mixture was evaporated, and the residue was separated directly by column chromatography (silica gel, 10:90 ethyl acetate-hexane) to give the compound of Example 51 as a viscous oil (7 mg, 0.019 mmol, 22%). TLC R<sub>f</sub> 0.55 (20:80 ethyl acetate-hexane). Spectral data: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.27 (1H, s), 7.60 (1H, d, J = 2.2 Hz), 7.43 (1H, dd, J = 8.0, 2.0 Hz), 7.32 (1H, d, J = 8.0 Hz), 3.84 (3H, s), 2.80-2.70 (1H, m), 2.08 (3H, s), 1.86-1.70 (4H, m), 0.82 (6H, t, J = 7.4 Hz). MS (NH<sub>3</sub>-CI): m/e

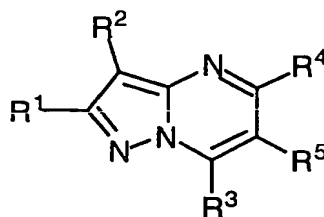
383 (2), 382 (12), 381 (14), 380 (65), 379 (25), 378 (100).

Examples 52-90 and 92 were and/or may be prepared according to the procedures described above. The

5 additional examples prepared or readily prepared (93-281) were (or may be) prepared according to the procedures described above and shown in the general schemes and described in the text. Table 1 shows the preferred compounds.

77

Table 1



<u>Ex</u> <u>No</u>	<u>R</u> <sup>1</sup>	<u>R</u> <sup>2</sup>	<u>R</u> <sup>4</sup>	<u>R</u> <sup>5</sup>	<u>R</u> <sup>3</sup>	<u>m.p.</u> <u>°C</u>
1	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	H	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	oil <sup>a</sup>
2	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	H	2-Cl-4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>	88- 89
3	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	H	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	oil <sup>b</sup>
4	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	H	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> - C <sub>6</sub> H <sub>2</sub>	166- 167
5	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	H	2-(CH <sub>3</sub> ) <sub>2</sub> N-4-CH <sub>3</sub> - pyridin-5-yl	-
6	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	CH <sub>3</sub>	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	90- 91
7	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	CH <sub>3</sub>	2-Cl-4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>	-
8	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	CH <sub>3</sub>	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-
9	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	CH <sub>3</sub>	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> - C <sub>6</sub> H <sub>2</sub>	-
10	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	CH <sub>3</sub>	2-(CH <sub>3</sub> ) <sub>2</sub> N-4-CH <sub>3</sub> - pyridin-5-yl	-
11	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	CH <sub>3</sub>	H	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-
12	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	CH <sub>3</sub>	H	2-Cl-4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>	-
13	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	CH <sub>3</sub>	H	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-
14	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	CH <sub>3</sub>	H	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> - C <sub>6</sub> H <sub>2</sub>	-
15	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	CH <sub>3</sub>	H	2-(CH <sub>3</sub> ) <sub>2</sub> N-4-CH <sub>3</sub> - pyridin-5-yl	-
16	C <sub>2</sub> H <sub>5</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> )CH	H	H	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	oil <sup>c</sup>
17	C <sub>2</sub> H <sub>5</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> )CH	H	H	2-Cl-4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>	-
18	C <sub>2</sub> H <sub>5</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> )CH	H	H	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	oil <sup>d</sup>
19	C <sub>2</sub> H <sub>5</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> )CH	H	H	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> - C <sub>6</sub> H <sub>2</sub>	-

78

20	C <sub>2</sub> H <sub>5</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> ) CH	H	H	2-(CH <sub>3</sub> ) <sub>2</sub> N-4-CH <sub>3</sub> - pyridin-5-yl	-
21	C <sub>2</sub> H <sub>5</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> ) CH	H	CH <sub>3</sub>	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	78- 79
22	C <sub>2</sub> H <sub>5</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> ) CH	H	CH <sub>3</sub>	2-Cl-4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>	-
23	C <sub>2</sub> H <sub>5</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> ) CH	H	CH <sub>3</sub>	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-
24	C <sub>2</sub> H <sub>5</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> ) CH	H	CH <sub>3</sub>	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> - C <sub>6</sub> H <sub>2</sub>	-
25	C <sub>2</sub> H <sub>5</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> ) CH	H	CH <sub>3</sub>	2-(CH <sub>3</sub> ) <sub>2</sub> N-4-CH <sub>3</sub> - pyridin-5-yl	-
26	C <sub>2</sub> H <sub>5</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> ) CH	CH <sub>3</sub>	H	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-
27	C <sub>2</sub> H <sub>5</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> ) CH	CH <sub>3</sub>	H	2-Cl-4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>	-
28	C <sub>2</sub> H <sub>5</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> ) CH	CH <sub>3</sub>	H	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-
29	C <sub>2</sub> H <sub>5</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> ) CH	CH <sub>3</sub>	H	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> - C <sub>6</sub> H <sub>2</sub>	-
30	C <sub>2</sub> H <sub>5</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> ) CH	CH <sub>3</sub>	H	2-(CH <sub>3</sub> ) <sub>2</sub> N-4-CH <sub>3</sub> - pyridin-5-yl	-
31	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	H	H	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	oil°
32	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	H	H	2-Cl-4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>	97- 98
33	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	H	H	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-
34	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	H	H	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> - C <sub>6</sub> H <sub>2</sub>	-
35	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	H	H	2-(CH <sub>3</sub> ) <sub>2</sub> N-4-CH <sub>3</sub> - pyridin-5-yl	-
36	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	H	CH <sub>3</sub>	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-
37	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	H	CH <sub>3</sub>	2-Cl-4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>	-
38	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	H	CH <sub>3</sub>	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-
39	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	H	CH <sub>3</sub>	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> - C <sub>6</sub> H <sub>2</sub>	-
40	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	H	CH <sub>3</sub>	2-(CH <sub>3</sub> ) <sub>2</sub> N-4-CH <sub>3</sub> - pyridin-5-yl	-
41	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	CH <sub>3</sub>	H	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-
42	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	CH <sub>3</sub>	H	2-Cl-4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>	-
43	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	CH <sub>3</sub>	H	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-
44	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	CH <sub>3</sub>	H	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> - C <sub>6</sub> H <sub>2</sub>	-



79

45	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	CH <sub>3</sub>	H	2-(CH <sub>3</sub> ) <sub>2</sub> N-4-CH <sub>3</sub> -pyridin-5-yl	-
46	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	H	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-
47	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	H	2-Cl-4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>	-
48	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	H	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-
49	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	H	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-
50	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	H	2-(CH <sub>3</sub> ) <sub>2</sub> N-4-CH <sub>3</sub> -pyridin-5-yl	-
51	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	CH <sub>3</sub>	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	oil <sup>t</sup>
52	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	CH <sub>3</sub>	2-Cl-4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>	-
53	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	CH <sub>3</sub>	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-
54	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	CH <sub>3</sub>	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-
55	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	CH <sub>3</sub>	2-(CH <sub>3</sub> ) <sub>2</sub> N-4-CH <sub>3</sub> -pyridin-5-yl	-
56	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	CH <sub>3</sub>	H	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-
57	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	CH <sub>3</sub>	H	2-Cl-4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>	-
58	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	CH <sub>3</sub>	H	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-
59	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	CH <sub>3</sub>	H	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-
60	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	CH <sub>3</sub>	H	2-(CH <sub>3</sub> ) <sub>2</sub> N-4-CH <sub>3</sub> -pyridin-5-yl	-
61	OCH <sub>3</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> )CH	H	H	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-
62	OCH <sub>3</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> )CH	H	H	2-Cl-4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>	-
63	OCH <sub>3</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> )CH	H	H	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-
64	OCH <sub>3</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> )CH	H	H	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-
65	OCH <sub>3</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> )CH	H	H	2-(CH <sub>3</sub> ) <sub>2</sub> N-4-CH <sub>3</sub> -pyridin-5-yl	-
66	OCH <sub>3</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> )CH	H	CH <sub>3</sub>	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-
67	OCH <sub>3</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> )CH	H	CH <sub>3</sub>	2-Cl-4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>	-
68	OCH <sub>3</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> )CH	H	CH <sub>3</sub>	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-
69	OCH <sub>3</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> )CH	H	CH <sub>3</sub>	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-
70	OCH <sub>3</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> )CH	H	CH <sub>3</sub>	2-(CH <sub>3</sub> ) <sub>2</sub> N-4-CH <sub>3</sub> -	-

80

						pyridin-5-yl	
71	OCH <sub>3</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> ) CH	CH <sub>3</sub>	H	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-	
72	OCH <sub>3</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> ) CH	CH <sub>3</sub>	H	2-Cl-4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>	-	
73	OCH <sub>3</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> ) CH	CH <sub>3</sub>	H	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-	
74	OCH <sub>3</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> ) CH	CH <sub>3</sub>	H	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> - C <sub>6</sub> H <sub>2</sub>	-	
75	OCH <sub>3</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> ) CH	CH <sub>3</sub>	H	2-(CH <sub>3</sub> ) <sub>2</sub> N-4-CH <sub>3</sub> - pyridin-5-yl	-	
76	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	H	H	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-	
77	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	H	H	2-Cl-4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>	-	
78	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	H	H	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-	
79	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	H	H	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> - C <sub>6</sub> H <sub>2</sub>	-	
80	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	H	H	2-(CH <sub>3</sub> ) <sub>2</sub> N-4-CH <sub>3</sub> - pyridin-5-yl	-	
81	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	H	CH <sub>3</sub>	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-	
82	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	H	CH <sub>3</sub>	2-Cl-4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>	-	
83	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	H	CH <sub>3</sub>	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-	
84	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	H	CH <sub>3</sub>	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> - C <sub>6</sub> H <sub>2</sub>	-	
85	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	H	CH <sub>3</sub>	2-(CH <sub>3</sub> ) <sub>2</sub> N-4-CH <sub>3</sub> - pyridin-5-yl	-	
86	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	CH <sub>3</sub>	H	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-	
87	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	CH <sub>3</sub>	H	2-Cl-4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>	-	
88	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	CH <sub>3</sub>	H	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-	
89	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	CH <sub>3</sub>	H	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> - C <sub>6</sub> H <sub>2</sub>	-	
90	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	CH <sub>3</sub>	H	2-(CH <sub>3</sub> ) <sub>2</sub> N-4-CH <sub>3</sub> - pyridin-5-yl	-	
91	CH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	H	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-	
92	OH	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	CH <sub>3</sub>	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	227- 228	
93	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	OCH <sub>3</sub>	H	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-	
94	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	OCH <sub>3</sub>	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-	
95	C <sub>2</sub> H <sub>5</sub>	C <sub>3</sub> H <sub>7</sub> (CH <sub>3</sub> ) CH	H	H	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-	
96	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> (c-C <sub>3</sub> H <sub>5</sub> ) CH	H	H	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-	

81

97	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> (c-C <sub>4</sub> H <sub>7</sub> ) CH	H	H	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-
98	C <sub>2</sub> H <sub>5</sub>	(c-C <sub>3</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	H	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-
99	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub> (c-C <sub>3</sub> H <sub>5</sub> ) CH	H	H	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-
100	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> (c-C <sub>4</sub> H <sub>7</sub> ) CH	H	H	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-
101	C <sub>2</sub> H <sub>5</sub>	(HOCH <sub>2</sub> ) <sub>2</sub> (CH <sub>3</sub> ) C	H	H	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-
102	C <sub>2</sub> H <sub>5</sub>	(HOCH <sub>2</sub> ) <sub>2</sub> (CH <sub>3</sub> ) C	H	H	2-Cl-4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>	-
103	C <sub>2</sub> H <sub>5</sub>	(HOCH <sub>2</sub> ) <sub>2</sub> (CH <sub>3</sub> ) C	H	H	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-
104	C <sub>2</sub> H <sub>5</sub>	(HOCH <sub>2</sub> ) <sub>2</sub> (CH <sub>3</sub> ) C	H	H	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> - C <sub>6</sub> H <sub>2</sub>	-
105	C <sub>2</sub> H <sub>5</sub>	(HOCH <sub>2</sub> ) <sub>2</sub> (CH <sub>3</sub> ) C	H	H	2-(CH <sub>3</sub> ) <sub>2</sub> N-4-CH <sub>3</sub> - pyridin-5-yl	-
106	C <sub>2</sub> H <sub>5</sub>	(HOCH <sub>2</sub> ) <sub>2</sub> (CH <sub>3</sub> ) C	H	H	2,4-Cl <sub>2</sub> -5-F-C <sub>6</sub> H <sub>2</sub>	-
107	C <sub>2</sub> H <sub>5</sub>	(HOCH <sub>2</sub> ) <sub>2</sub> (CH <sub>3</sub> ) C	H	H	2-Cl-4-OCH <sub>3</sub> -5-F	-
108	C <sub>2</sub> H <sub>5</sub>	(HOCH <sub>2</sub> ) <sub>2</sub> (CH <sub>3</sub> ) C	H	H	2-Cl-4,5-(OCH <sub>3</sub> ) <sub>2</sub>	-
109	C <sub>2</sub> H <sub>5</sub>	(CH <sub>3</sub> OCH <sub>2</sub> ) <sub>2</sub> (CH <sub>3</sub> ) C	H	H	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-
110	C <sub>2</sub> H <sub>5</sub>	(CH <sub>3</sub> OCH <sub>2</sub> ) <sub>2</sub> (CH <sub>3</sub> ) C	H	H	2-Cl-4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>	-
111	C <sub>2</sub> H <sub>5</sub>	(CH <sub>3</sub> OCH <sub>2</sub> ) <sub>2</sub> (CH <sub>3</sub> ) C	H	H	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-
112	C <sub>2</sub> H <sub>5</sub>	(CH <sub>3</sub> OCH <sub>2</sub> ) <sub>2</sub> (CH <sub>3</sub> ) C	H	H	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> - C <sub>6</sub> H <sub>2</sub>	-
113	C <sub>2</sub> H <sub>5</sub>	(CH <sub>3</sub> OCH <sub>2</sub> ) <sub>2</sub> (CH <sub>3</sub> ) C	H	H	2-(CH <sub>3</sub> ) <sub>2</sub> N-4-CH <sub>3</sub> - pyridin-5-yl	-
114	C <sub>2</sub> H <sub>5</sub>	(CH <sub>3</sub> OCH <sub>2</sub> ) <sub>2</sub> (CH <sub>3</sub> ) C	H	H	2,4-Cl <sub>2</sub> -5-F-C <sub>6</sub> H <sub>2</sub>	-
115	C <sub>2</sub> H <sub>5</sub>	(CH <sub>3</sub> OCH <sub>2</sub> ) <sub>2</sub> (CH <sub>3</sub> ) C	H	H	2-Cl-4-OCH <sub>3</sub> -5-F	-
116	C <sub>2</sub> H <sub>5</sub>	(CH <sub>3</sub> OCH <sub>2</sub> ) <sub>2</sub> (CH <sub>3</sub> ) C	H	H	2-Cl-4,5-(OCH <sub>3</sub> ) <sub>2</sub>	-
117	C <sub>2</sub> H <sub>5</sub>	(H <sub>2</sub> C=CH) <sub>2</sub> (CH <sub>3</sub> ) C	H	H	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-

82

118	C <sub>2</sub> H <sub>5</sub>	(H <sub>2</sub> C=CH) <sub>2</sub> (CH <sub>3</sub> )C	H	H	2-Cl-4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>	-
119	C <sub>2</sub> H <sub>5</sub>	(H <sub>2</sub> C=CH) <sub>2</sub> (CH <sub>3</sub> )C	H	H	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-
120	C <sub>2</sub> H <sub>5</sub>	(H <sub>2</sub> C=CH) <sub>2</sub> (CH <sub>3</sub> )C	H	H	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> - C <sub>6</sub> H <sub>2</sub>	-
121	C <sub>2</sub> H <sub>5</sub>	(H <sub>2</sub> C=CH) <sub>2</sub> (CH <sub>3</sub> )C	H	H	2-(CH <sub>3</sub> ) <sub>2</sub> N-4-CH <sub>3</sub> - pyridin-5-yl	-
122	C <sub>2</sub> H <sub>5</sub>	(H <sub>2</sub> C=CH) <sub>2</sub> (CH <sub>3</sub> )C	H	H	2,4-Cl <sub>2</sub> -5-F-C <sub>6</sub> H <sub>2</sub>	-
123	C <sub>2</sub> H <sub>5</sub>	(H <sub>2</sub> C=CH) <sub>2</sub> (CH <sub>3</sub> )C	H	H	2-Cl-4-OCH <sub>3</sub> -5-F	-
124	C <sub>2</sub> H <sub>5</sub>	(H <sub>2</sub> C=CH) <sub>2</sub> (CH <sub>3</sub> )C	H	H	2-Cl-4,5-(OCH <sub>3</sub> ) <sub>2</sub>	-
125	C <sub>2</sub> H <sub>5</sub>	(c-C <sub>3</sub> H <sub>5</sub> ) <sub>2</sub> (CH <sub>3</sub> )C	H	H	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-
126	C <sub>2</sub> H <sub>5</sub>	(c-C <sub>3</sub> H <sub>5</sub> ) <sub>2</sub> (CH <sub>3</sub> )C	H	H	2-Cl-4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>	-
127	C <sub>2</sub> H <sub>5</sub>	(c-C <sub>3</sub> H <sub>5</sub> ) <sub>2</sub> (CH <sub>3</sub> )C	H	H	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-
128	C <sub>2</sub> H <sub>5</sub>	(c-C <sub>3</sub> H <sub>5</sub> ) <sub>2</sub> (CH <sub>3</sub> )C	H	H	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> - C <sub>6</sub> H <sub>2</sub>	-
129	C <sub>2</sub> H <sub>5</sub>	(c-C <sub>3</sub> H <sub>5</sub> ) <sub>2</sub> (CH <sub>3</sub> )C	H	H	2-(CH <sub>3</sub> ) <sub>2</sub> N-4-CH <sub>3</sub> - pyridin-5-yl	-
130	C <sub>2</sub> H <sub>5</sub>	(c-C <sub>3</sub> H <sub>5</sub> ) <sub>2</sub> (CH <sub>3</sub> )C	H	H	2,4-Cl <sub>2</sub> -5-F-C <sub>6</sub> H <sub>2</sub>	-
131	C <sub>2</sub> H <sub>5</sub>	(c-C <sub>3</sub> H <sub>5</sub> ) <sub>2</sub> (CH <sub>3</sub> )C	H	H	2-Cl-4-OCH <sub>3</sub> -5-F	-
132	C <sub>2</sub> H <sub>5</sub>	(c-C <sub>3</sub> H <sub>5</sub> ) <sub>2</sub> (CH <sub>3</sub> )C	H	H	2-Cl-4,5-(OCH <sub>3</sub> ) <sub>2</sub>	-
133	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> (OH)C	H	H	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-
134	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> (OH)C	H	H	2-Cl-4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>	-
135	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> (OH)C	H	H	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-
136	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> (OH)C	H	H	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> - C <sub>6</sub> H <sub>2</sub>	-
137	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> (OH)C	H	H	2-(CH <sub>3</sub> ) <sub>2</sub> N-4-CH <sub>3</sub> - pyridin-5-yl	-
138	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> (OH)C	H	H	2,4-Cl <sub>2</sub> -5-F-C <sub>6</sub> H <sub>2</sub>	-

83

139	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> (OH)C	H	H	2-Cl-4-OCH <sub>3</sub> -5-F	-
140	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> (OH)C	H	H	2-Cl-4,5-(OCH <sub>3</sub> ) <sub>2</sub>	-
141	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub> (OCH <sub>3</sub> )CH	H	H	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-
142	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub> (OCH <sub>3</sub> )CH	H	H	2-Cl-4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>	-
143	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub> (OCH <sub>3</sub> )CH	H	H	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-
144	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub> (OCH <sub>3</sub> )CH	H	H	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> - C <sub>6</sub> H <sub>2</sub>	-
145	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub> (OCH <sub>3</sub> )CH	H	H	2-(CH <sub>3</sub> ) <sub>2</sub> N-4-CH <sub>3</sub> - pyridin-5-yl	-
146	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub> (OCH <sub>3</sub> )CH	H	H	2,4-Cl <sub>2</sub> -5-F-C <sub>6</sub> H <sub>2</sub>	-
147	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub> (OCH <sub>3</sub> )CH	H	H	2-Cl-4-OCH <sub>3</sub> -5-F	-
148	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub> (OCH <sub>3</sub> )CH	H	H	2-Cl-4,5-(OCH <sub>3</sub> ) <sub>2</sub>	-
149	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	H	2,4-Cl <sub>2</sub> -5-F-C <sub>6</sub> H <sub>2</sub>	oil
150	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	H	2-Cl-4-OCH <sub>3</sub> -5-F	-
151	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	H	2-Cl-4,5-(OCH <sub>3</sub> ) <sub>2</sub>	-
152	C <sub>2</sub> H <sub>5</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> )CH	H	H	2,4-Cl <sub>2</sub> -5-F-C <sub>6</sub> H <sub>2</sub>	-
153	C <sub>2</sub> H <sub>5</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> )CH	H	H	2-Cl-4-OCH <sub>3</sub> -5-F	-
154	C <sub>2</sub> H <sub>5</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> )CH	H	H	2-Cl-4,5-(OCH <sub>3</sub> ) <sub>2</sub>	-
155	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	H	2,4-Cl <sub>2</sub> -5-F-C <sub>6</sub> H <sub>2</sub>	oil <sup>o</sup>
156	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	H	2-Cl-4-OCH <sub>3</sub> -5-F	-
157	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	H	2-Cl-4,5-(OCH <sub>3</sub> ) <sub>2</sub>	-
158	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	H	H	2,4-Cl <sub>2</sub> -5-F-C <sub>6</sub> H <sub>2</sub>	-
159	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	H	H	2-Cl-4-OCH <sub>3</sub> -5-F	-
160	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	H	H	2-Cl-4,5-(OCH <sub>3</sub> ) <sub>2</sub>	-
161	C <sub>2</sub> H <sub>5</sub>	C <sub>3</sub> H <sub>7</sub> (CH <sub>3</sub> )CH	H	H	2-Cl-4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>	-
162	C <sub>2</sub> H <sub>5</sub>	C <sub>3</sub> H <sub>7</sub> (CH <sub>3</sub> )CH	H	H	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-
163	C <sub>2</sub> H <sub>5</sub>	C <sub>3</sub> H <sub>7</sub> (CH <sub>3</sub> )CH	H	H	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> - C <sub>6</sub> H <sub>2</sub>	-
164	C <sub>2</sub> H <sub>5</sub>	C <sub>3</sub> H <sub>7</sub> (CH <sub>3</sub> )CH	H	H	2-(CH <sub>3</sub> ) <sub>2</sub> N-4-CH <sub>3</sub> - pyridin-5-yl	-
165	C <sub>2</sub> H <sub>5</sub>	C <sub>3</sub> H <sub>7</sub> (CH <sub>3</sub> )CH	H	H	2,4-Cl <sub>2</sub> -5-F-C <sub>6</sub> H <sub>2</sub>	-
166	C <sub>2</sub> H <sub>5</sub>	C <sub>3</sub> H <sub>7</sub> (CH <sub>3</sub> )CH	H	H	2-Cl-4-OCH <sub>3</sub> -5-F	-
167	C <sub>2</sub> H <sub>5</sub>	C <sub>3</sub> H <sub>7</sub> (CH <sub>3</sub> )CH	H	H	2-Cl-4,5-(OCH <sub>3</sub> ) <sub>2</sub>	-
168	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	H	2-CH <sub>3</sub> -4-OCH <sub>3</sub> -5-	-

84

					F-C <sub>6</sub> H <sub>2</sub>	
169	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	H	2-CH <sub>3</sub> -4-OCH <sub>3</sub> -5-	-
					F-C <sub>6</sub> H <sub>2</sub>	
170	C <sub>2</sub> H <sub>5</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> )CH	H	H	2-CH <sub>3</sub> -4-OCH <sub>3</sub> -5-	-
					F-C <sub>6</sub> H <sub>2</sub>	
171	OCH <sub>3</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> )CH	H	H	2-CH <sub>3</sub> -4-OCH <sub>3</sub> -5-	-
					F-C <sub>6</sub> H <sub>2</sub>	
172	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	H	H	2-CH <sub>3</sub> -4-OCH <sub>3</sub> -5-	-
					F-C <sub>6</sub> H <sub>2</sub>	
173	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	H	H	2-CH <sub>3</sub> -4-OCH <sub>3</sub> -5-	-
					F-C <sub>6</sub> H <sub>2</sub>	
174	C <sub>2</sub> H <sub>5</sub>	C <sub>3</sub> H <sub>7</sub> (CH <sub>3</sub> )CH	H	H	2-CH <sub>3</sub> -4-OCH <sub>3</sub> -5-	-
					F-C <sub>6</sub> H <sub>2</sub>	
175	OCH <sub>3</sub>	C <sub>3</sub> H <sub>7</sub> (CH <sub>3</sub> )CH	H	H	2-CH <sub>3</sub> -4-OCH <sub>3</sub> -5-	-
					F-C <sub>6</sub> H <sub>2</sub>	
176	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub> (OCH <sub>3</sub> )CH	H	H	2-CH <sub>3</sub> -4-OCH <sub>3</sub> -5-	-
					F-C <sub>6</sub> H <sub>2</sub>	
177	OCH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub> (OCH <sub>3</sub> )CH	H	H	2-CH <sub>3</sub> -4-OCH <sub>3</sub> -5-	-
					F-C <sub>6</sub> H <sub>2</sub>	
178	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	H	2-CH <sub>3</sub> -4-OCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	-
179	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	H	2-CH <sub>3</sub> -4-OCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	-
180	C <sub>2</sub> H <sub>5</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> )CH	H	H	2-CH <sub>3</sub> -4-OCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	-
181	OCH <sub>3</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> )CH	H	H	2-CH <sub>3</sub> -4-OCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	-
182	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	H	H	2-CH <sub>3</sub> -4-OCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	-
183	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	H	H	2-CH <sub>3</sub> -4-OCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	-
184	C <sub>2</sub> H <sub>5</sub>	C <sub>3</sub> H <sub>7</sub> (CH <sub>3</sub> )CH	H	H	2-CH <sub>3</sub> -4-OCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	-
185	OCH <sub>3</sub>	C <sub>3</sub> H <sub>7</sub> (CH <sub>3</sub> )CH	H	H	2-CH <sub>3</sub> -4-OCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	-
186	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub> (OCH <sub>3</sub> )CH	H	H	2-CH <sub>3</sub> -4-OCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	-
187	OCH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub> (OCH <sub>3</sub> )CH	H	H	2-CH <sub>3</sub> -4-OCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	-
188	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	H	2-CH <sub>3</sub> -4-Cl-C <sub>6</sub> H <sub>3</sub>	-
189	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	H	2-CH <sub>3</sub> -4-Cl-C <sub>6</sub> H <sub>3</sub>	-
190	C <sub>2</sub> H <sub>5</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> )CH	H	H	2-CH <sub>3</sub> -4-Cl-C <sub>6</sub> H <sub>3</sub>	-
191	OCH <sub>3</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> )CH	H	H	2-CH <sub>3</sub> -4-Cl-C <sub>6</sub> H <sub>3</sub>	-

85

192	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	H	H	2-CH <sub>3</sub> -4-Cl-C <sub>6</sub> H <sub>3</sub>	-
193	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	H	H	2-CH <sub>3</sub> -4-Cl-C <sub>6</sub> H <sub>3</sub>	-
194	C <sub>2</sub> H <sub>5</sub>	C <sub>3</sub> H <sub>7</sub> (CH <sub>3</sub> ) CH	H	H	2-CH <sub>3</sub> -4-Cl-C <sub>6</sub> H <sub>3</sub>	-
195	OCH <sub>3</sub>	C <sub>3</sub> H <sub>7</sub> (CH <sub>3</sub> ) CH	H	H	2-CH <sub>3</sub> -4-Cl-C <sub>6</sub> H <sub>3</sub>	-
196	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub> (OCH <sub>3</sub> ) CH	H	H	2-CH <sub>3</sub> -4-Cl-C <sub>6</sub> H <sub>3</sub>	-
197	OCH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub> (OCH <sub>3</sub> ) CH	H	H	2-CH <sub>3</sub> -4-Cl-C <sub>6</sub> H <sub>3</sub>	-
198	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> OCH <sub>2</sub> (CH <sub>3</sub> ) C H	H	H	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	oil <sup>b</sup>
199	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> OCH <sub>2</sub> (CH <sub>3</sub> ) C H	H	H	2-Cl-4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>	-
200	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> OCH <sub>2</sub> (CH <sub>3</sub> ) C H	H	H	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-
201	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> OCH <sub>2</sub> (CH <sub>3</sub> ) C H	H	H	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> - C <sub>6</sub> H <sub>2</sub>	-
202	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> OCH <sub>2</sub> (CH <sub>3</sub> ) C H	H	H	2-(CH <sub>3</sub> ) <sub>2</sub> N-4-CH <sub>3</sub> - pyridin-5-yl	-
203	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> OCH <sub>2</sub> (CH <sub>3</sub> ) C H	H	H	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> - C <sub>6</sub> H <sub>2</sub>	-
204	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> OCH <sub>2</sub> (CH <sub>3</sub> ) C H	H	H	2,4-Cl <sub>2</sub> -5-F-C <sub>6</sub> H <sub>2</sub>	-
205	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> OCH <sub>2</sub> (CH <sub>3</sub> ) C H	H	H	2-Cl-4-OCH <sub>3</sub> -5-F	-
206	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> OCH <sub>2</sub> (CH <sub>3</sub> ) C H	H	H	2-Cl-4,5-(OCH <sub>3</sub> ) <sub>2</sub>	-
207	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> OCH <sub>2</sub> (CH <sub>3</sub> ) C H	H	H	2-CH <sub>3</sub> -4-OCH <sub>3</sub> -5- F-C <sub>6</sub> H <sub>2</sub>	-
208	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> OCH <sub>2</sub> (CH <sub>3</sub> ) C H	H	H	2-CH <sub>3</sub> -4-OCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	-
209	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> OCH <sub>2</sub> (CH <sub>3</sub> ) C H	H	H	2-CH <sub>3</sub> -4-Cl-C <sub>6</sub> H <sub>3</sub>	-
210	OCH <sub>3</sub>	CH <sub>3</sub> OCH <sub>2</sub> (CH <sub>3</sub> ) C H	H	H	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-
211	OCH <sub>3</sub>	CH <sub>3</sub> OCH <sub>2</sub> (CH <sub>3</sub> ) C H	H	H	2-Cl-4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>	-
212	OCH <sub>3</sub>	CH <sub>3</sub> OCH <sub>2</sub> (CH <sub>3</sub> ) C H	H	H	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-
213	OCH <sub>3</sub>	CH <sub>3</sub> OCH <sub>2</sub> (CH <sub>3</sub> ) C H	H	H	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> - C <sub>6</sub> H <sub>2</sub>	-
214	OCH <sub>3</sub>	CH <sub>3</sub> OCH <sub>2</sub> (CH <sub>3</sub> ) C H	H	H	2-(CH <sub>3</sub> ) <sub>2</sub> N-4-CH <sub>3</sub> - pyridin-5-yl	-
215	OCH <sub>3</sub>	CH <sub>3</sub> OCH <sub>2</sub> (CH <sub>3</sub> ) C H	H	H	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> - C <sub>6</sub> H <sub>2</sub>	-

86

216	OCH <sub>3</sub>	CH <sub>3</sub> OCH <sub>2</sub> (CH <sub>3</sub> )C H	H	H	2,4-Cl <sub>2</sub> -5-F-C <sub>6</sub> H <sub>2</sub>	-
217	OCH <sub>3</sub>	CH <sub>3</sub> OCH <sub>2</sub> (CH <sub>3</sub> )C H	H	H	2-Cl-4-OCH <sub>3</sub> -5-F	-
218	OCH <sub>3</sub>	CH <sub>3</sub> OCH <sub>2</sub> (CH <sub>3</sub> )C H	H	H	2-Cl-4,5-(OCH <sub>3</sub> ) <sub>2</sub>	-
219	OCH <sub>3</sub>	CH <sub>3</sub> OCH <sub>2</sub> (CH <sub>3</sub> )C H	H	H	2-CH <sub>3</sub> -4-OCH <sub>3</sub> -5- F-C <sub>6</sub> H <sub>2</sub>	-
220	OCH <sub>3</sub>	CH <sub>3</sub> OCH <sub>2</sub> (CH <sub>3</sub> )C H	H	H	2-CH <sub>3</sub> -4-OCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	-
221	OCH <sub>3</sub>	CH <sub>3</sub> OCH <sub>2</sub> (CH <sub>3</sub> )C H	H	H	2-CH <sub>3</sub> -4-Cl-C <sub>6</sub> H <sub>3</sub>	-
222	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub> OCH <sub>2</sub> (CH <sub>3</sub> )C H	H	H	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-
223	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub> OCH <sub>2</sub> (CH <sub>3</sub> )C H	H	H	2-Cl-4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>	-
224	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub> OCH <sub>2</sub> (CH <sub>3</sub> )C H	H	H	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-
225	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub> OCH <sub>2</sub> (CH <sub>3</sub> )C H	H	H	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> - C <sub>6</sub> H <sub>2</sub>	-
226	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub> OCH <sub>2</sub> (CH <sub>3</sub> )C H	H	H	2-(CH <sub>3</sub> ) <sub>2</sub> N-4-CH <sub>3</sub> - pyridin-5-yl	-
227	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub> OCH <sub>2</sub> (CH <sub>3</sub> )C H	H	H	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> - C <sub>6</sub> H <sub>2</sub>	-
228	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub> OCH <sub>2</sub> (CH <sub>3</sub> )C H	H	H	2,4-Cl <sub>2</sub> -5-F-C <sub>6</sub> H <sub>2</sub>	-
229	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub> OCH <sub>2</sub> (CH <sub>3</sub> )C H	H	H	2-Cl-4-OCH <sub>3</sub> -5-F	-
230	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub> OCH <sub>2</sub> (CH <sub>3</sub> )C H	H	H	2-Cl-4,5-(OCH <sub>3</sub> ) <sub>2</sub>	-
231	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub> OCH <sub>2</sub> (CH <sub>3</sub> )C H	H	H	2-CH <sub>3</sub> -4-OCH <sub>3</sub> -5- F-C <sub>6</sub> H <sub>2</sub>	-
232	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub> OCH <sub>2</sub> (CH <sub>3</sub> )C H	H	H	2-CH <sub>3</sub> -4-OCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	-
233	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub> OCH <sub>2</sub> (CH <sub>3</sub> )C H	H	H	2-CH <sub>3</sub> -4-Cl-C <sub>6</sub> H <sub>3</sub>	-
234	OCH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub> OCH <sub>2</sub> (CH <sub>3</sub> )C H	H	H	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-
235	OCH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub> OCH <sub>2</sub> (CH <sub>3</sub> )C H	H	H	2-Cl-4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>	-
236	OCH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub> OCH <sub>2</sub> (CH <sub>3</sub> )C H	H	H	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-
237	OCH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub> OCH <sub>2</sub> (CH <sub>3</sub> )C H	H	H	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> - C <sub>6</sub> H <sub>2</sub>	-
238	OCH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub> OCH <sub>2</sub> (CH <sub>3</sub> )C	H	H	2-(CH <sub>3</sub> ) <sub>2</sub> N-4-CH <sub>3</sub> -	-



		H			pyridin-5-yl	
239	OCH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub> OCH <sub>2</sub> (CH <sub>3</sub> )C H	H	H	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> - C <sub>6</sub> H <sub>2</sub>	-
240	OCH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub> OCH <sub>2</sub> (CH <sub>3</sub> )C H	H	H	2,4-Cl <sub>2</sub> -5-F-C <sub>6</sub> H <sub>2</sub>	-
241	OCH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub> OCH <sub>2</sub> (CH <sub>3</sub> )C H	H	H	2-Cl-4-OCH <sub>3</sub> -5-F	-
242	OCH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub> OCH <sub>2</sub> (CH <sub>3</sub> )C H	H	H	2-Cl-4,5-(OCH <sub>3</sub> ) <sub>2</sub>	-
243	OCH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub> OCH <sub>2</sub> (CH <sub>3</sub> )C H	H	H	2-CH <sub>3</sub> -4-OCH <sub>3</sub> -5- F-C <sub>6</sub> H <sub>2</sub>	-
244	OCH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub> OCH <sub>2</sub> (CH <sub>3</sub> )C H	H	H	2-CH <sub>3</sub> -4-OCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	-
245	OCH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub> OCH <sub>2</sub> (CH <sub>3</sub> )C H	H	H	2-CH <sub>3</sub> -4-Cl-C <sub>6</sub> H <sub>3</sub>	-
246	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> OCH <sub>2</sub> (C <sub>2</sub> H <sub>5</sub> )C H	H	H	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-
247	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> OCH <sub>2</sub> (C <sub>2</sub> H <sub>5</sub> )C H	H	H	2-Cl-4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>	-
248	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> OCH <sub>2</sub> (C <sub>2</sub> H <sub>5</sub> )C H	H	H	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-
249	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> OCH <sub>2</sub> (C <sub>2</sub> H <sub>5</sub> )C H	H	H	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> - C <sub>6</sub> H <sub>2</sub>	-
250	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> OCH <sub>2</sub> (C <sub>2</sub> H <sub>5</sub> )C H	H	H	2-(CH <sub>3</sub> ) <sub>2</sub> N-4-CH <sub>3</sub> - pyridin-5-yl	-
251	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> OCH <sub>2</sub> (C <sub>2</sub> H <sub>5</sub> )C H	H	H	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> - C <sub>6</sub> H <sub>2</sub>	-
252	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> OCH <sub>2</sub> (C <sub>2</sub> H <sub>5</sub> )C H	H	H	2,4-Cl <sub>2</sub> -5-F-C <sub>6</sub> H <sub>2</sub>	-
253	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> OCH <sub>2</sub> (C <sub>2</sub> H <sub>5</sub> )C H	H	H	2-Cl-4-OCH <sub>3</sub> -5-F	-
254	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> OCH <sub>2</sub> (C <sub>2</sub> H <sub>5</sub> )C H	H	H	2-Cl-4,5-(OCH <sub>3</sub> ) <sub>2</sub>	-
255	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> OCH <sub>2</sub> (C <sub>2</sub> H <sub>5</sub> )C H	H	H	2-CH <sub>3</sub> -4-OCH <sub>3</sub> -5- F-C <sub>6</sub> H <sub>2</sub>	-
256	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> OCH <sub>2</sub> (C <sub>2</sub> H <sub>5</sub> )C H	H	H	2-CH <sub>3</sub> -4-OCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	-
257	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> OCH <sub>2</sub> (C <sub>2</sub> H <sub>5</sub> )C H	H	H	2-CH <sub>3</sub> -4-Cl-C <sub>6</sub> H <sub>3</sub>	-
258	OCH <sub>3</sub>	CH <sub>3</sub> OCH <sub>2</sub> (C <sub>2</sub> H <sub>5</sub> )C H	H	H	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-
259	OCH <sub>3</sub>	CH <sub>3</sub> OCH <sub>2</sub> (C <sub>2</sub> H <sub>5</sub> )C H	H	H	2-Cl-4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>3</sub>	-
260	OCH <sub>3</sub>	CH <sub>3</sub> OCH <sub>2</sub> (C <sub>2</sub> H <sub>5</sub> )C H	H	H	2,4,6-(CH <sub>3</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>2</sub>	-

~~88~~

261	OCH <sub>3</sub>	CH <sub>3</sub> OCH <sub>2</sub> (C <sub>2</sub> H <sub>5</sub> )C H	H	H	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> - C <sub>6</sub> H <sub>2</sub>	-
262	OCH <sub>3</sub>	CH <sub>3</sub> OCH <sub>2</sub> (C <sub>2</sub> H <sub>5</sub> )C H	H	H	2-(CH <sub>3</sub> ) <sub>2</sub> N-4-CH <sub>3</sub> - pyridin-5-yl	-
263	OCH <sub>3</sub>	CH <sub>3</sub> OCH <sub>2</sub> (C <sub>2</sub> H <sub>5</sub> )C H	H	H	2,4,6-(OCH <sub>3</sub> ) <sub>3</sub> - C <sub>6</sub> H <sub>2</sub>	-
264	OCH <sub>3</sub>	CH <sub>3</sub> OCH <sub>2</sub> (C <sub>2</sub> H <sub>5</sub> )C H	H	H	2,4-Cl <sub>2</sub> -5-F-C <sub>6</sub> H <sub>2</sub>	-
265	OCH <sub>3</sub>	CH <sub>3</sub> OCH <sub>2</sub> (C <sub>2</sub> H <sub>5</sub> )C H	H	H	2-Cl-4-OCH <sub>3</sub> -5-F	-
266	OCH <sub>3</sub>	CH <sub>3</sub> OCH <sub>2</sub> (C <sub>2</sub> H <sub>5</sub> )C H	H	H	2-Cl-4,5-(OCH <sub>3</sub> ) <sub>2</sub>	-
267	OCH <sub>3</sub>	CH <sub>3</sub> OCH <sub>2</sub> (C <sub>2</sub> H <sub>5</sub> )C H	H	H	2-CH <sub>3</sub> -4-OCH <sub>3</sub> -5- F-C <sub>6</sub> H <sub>2</sub>	-
268	OCH <sub>3</sub>	CH <sub>3</sub> OCH <sub>2</sub> (C <sub>2</sub> H <sub>5</sub> )C H	H	H	2-CH <sub>3</sub> -4-OCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	-
269	OCH <sub>3</sub>	CH <sub>3</sub> OCH <sub>2</sub> (C <sub>2</sub> H <sub>5</sub> )C H	H	H	2-CH <sub>3</sub> -4-Cl-C <sub>6</sub> H <sub>3</sub>	-
270	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	H	2-Cl-4-CF <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	oil <sup>i</sup>
271	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	H	2-Cl-4-CF <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	-
272	C <sub>2</sub> H <sub>5</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> )CH	H	H	2-Cl-4-CF <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	-
273	OCH <sub>3</sub>	C <sub>4</sub> H <sub>9</sub> (C <sub>2</sub> H <sub>5</sub> )CH	H	H	2-Cl-4-CF <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	-
274	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	H	H	2-Cl-4-CF <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	-
275	OCH <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	H	H	2-Cl-4-CF <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	-
276	C <sub>2</sub> H <sub>5</sub>	C <sub>3</sub> H <sub>7</sub> (CH <sub>3</sub> )CH	H	H	2-Cl-4-CF <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	-
277	OCH <sub>3</sub>	C <sub>3</sub> H <sub>7</sub> (CH <sub>3</sub> )CH	H	H	2-Cl-4-CF <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	-
278	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub> (OCH <sub>3</sub> )CH	H	H	2-Cl-4-CF <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	-
279	OCH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub> (OCH <sub>3</sub> )CH	H	H	2-Cl-4-CF <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	-
280	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> OCH <sub>2</sub> (CH <sub>3</sub> )C H	H	H	2-Cl-4-CF <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	-
281	OCH <sub>3</sub>	CH <sub>3</sub> OCH <sub>2</sub> (CH <sub>3</sub> )C H	H	H	2-Cl-4-CF <sub>3</sub> -C <sub>6</sub> H <sub>3</sub>	-

Key:

- a) Spectral data for Example 1: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ
- 5 8.38 (1H, d, J = 4.1 Hz), 7.58 (1H, d, J = 2.0 Hz), 7.55 (1H, d, J = 8.2 Hz), 7.41 (1H, dd, J = 8.2, 2.0 Hz), 6.65 (1H, d, J = 4.1 Hz), 2.79 (2H, q, J = 7.7 Hz), 2.78-2.68

89

- (1H, m), 2.03-1.79 (4H, m), 1.25 (3H, t,  $J = 7.7$  Hz), 0.83 (6H, t,  $J = 7.3$  Hz). MS ( $\text{NH}_3\text{-CI}$ ):  $m/e$  367 (2), 366 (11), 365 (15), 364 (65), 363 (25), 362 (100). Analysis calc'd for  $\text{C}_{19}\text{H}_{21}\text{Cl}_2\text{N}_3$ : C, 62.99; H, 5.84; N, 11.60; found: C, 62.97; H, 5.74; N, 11.49.
- b) Spectral data for Example 3:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.36 (1H, d,  $J = 5.0$  Hz), 7.00 (2H, s), 6.50 (1H, d,  $J = 5.0$  Hz), 2.77 (2H, q,  $J = 7.7$  Hz), 2.76-2.66 (1H, m), 2.36 (3H, s), 2.02 (6H, s), 2.00-1.80 (4H, m), 1.21 (3H, t,  $J = 7.7$  Hz), 0.83 (6H, t,  $J = 7.5$  Hz). MS ( $\text{NH}_3\text{-CI}$ ):  $m/e$  338 (3), 337 (24), 336 (100). Analysis calc'd for  $\text{C}_{22}\text{H}_{29}\text{N}_3$ : C, 78.76; H, 8.71; N, 12.53; found: C, 78.74; H, 8.74; N, 12.41.
- c) Spectral data for Example 16:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.39 (1H, d,  $J = 4.2$  Hz), 7.59 (1H, d,  $J = 8.3$  Hz), 7.58 (1H, d,  $J = 2.0$  Hz), 7.42 (1H, dd,  $J = 8.3, 2.0$  Hz), 6.65 (1H, d,  $J = 4.2$  Hz), 2.82-2.72 (1H, m), 2.79 (2H, q,  $J = 7.3$  Hz), 2.00-1.77 (4H, m), 1.35-1.10 (4H, m), 1.25 (3H, t,  $J = 7.3$  Hz), 0.83 (3H, t,  $J = 7.0$  Hz), 0.82 (3H, t,  $J = 7.5$  Hz). MS ( $\text{NH}_3\text{-CI}$ ):  $m/e$  calculated for  $\text{C}_{21}\text{H}_{26}\text{Cl}_2\text{N}_3$ : 390.1504, found 390.1502; 395 (3), 394 (12), 393 (17), 392 (67), 391 (29), 390 (100).
- d) Spectral data for Example 18:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.36 (1H, d,  $J = 4.0$  Hz), 7.00 (2H, s), 6.50 (1H, d,  $J = 4.0$  Hz), 2.82-2.73 (1H, m), 2.77 (2H, q,  $J = 7.6$  Hz), 2.36 (3H, s), 2.02 (3H, s), 2.01 (3H, s), 2.00-1.78 (4H, m), 1.38-1.09 (4H, m), 1.20 (3H, t,  $J = 7.6$  Hz), 0.83 (3H, t,  $J = 7.0$  Hz), 0.81 (3H, t,  $J = 7.3$  Hz). MS ( $\text{NH}_3\text{-CI}$ ):  $m/e$  calc'd for  $\text{C}_{24}\text{H}_{34}\text{N}_3$ : 364.2753, found 364.2754; 366 (4), 365 (27), 364 (100).
- e) Spectral data for Example 31:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.38 (1H, d,  $J = 4.0$  Hz), 7.58 (1H, d,  $J = 1.8$  Hz), 7.56 (1H, d,  $J = 8.4$  Hz), 7.42 (1H, dd,  $J = 8.4, 1.8$  Hz), 6.65

90

(1H, d,  $J = 4.0$  Hz), 3.27 (4H, q,  $J = 7.3$  Hz), 2.80 (2H, q,  $J = 7.3$  Hz), 1.26 (3H, t,  $J = 7.3$  Hz), 1.00 (6H, t,  $J = 7.3$  Hz). MS ( $\text{NH}_3\text{-CI}$ ): calculated for  $\text{C}_{18}\text{H}_{21}\text{Cl}_2\text{N}_4$ : 363.1143, found 363.1146; m/e 367 (6), 366 (14), 365 (81), 364

5 (28), 363 (100).

f) Spectral data for Example 51:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.27 (1H, s), 7.60 (1H, d,  $J = 2.2$  Hz), 7.43 (1H, dd,  $J = 8.0, 2.0$  Hz), 7.32 (1H, d,  $J = 8.0$  Hz), 3.84 (3H, s), 2.80-2.70 (1H, m), 2.08 (3H, s), 1.86-1.70 (4H, m), 0.82  
10 (6H, t,  $J = 7.4$  Hz). MS ( $\text{NH}_3\text{-CI}$ ): m/e 383 (2), 382 (12), 381 (14), 380 (65), 379 (25), 378 (100).

g) Spectral data for Example 155:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.39 (1H, d,  $J = 4.0$  Hz), 7.63 (1H, d,  $J = 6.6$  Hz), 7.48 (1H, d,  $J = 8.8$  Hz), 6.67 (1H, d,  $J = 4.0$  Hz), 2.79  
15 (2H, q,  $J = 7.4$  Hz), 2.78-2.68 (1H, m), 2.03-1.79 (4H, m), 1.26 (3H, t,  $J = 7.4$  Hz), 0.83 (6H, t,  $J = 7.5$  Hz). MS ( $\text{NH}_3\text{-CI}$ ): m/e 384 (11), 383 (16), 382 (79), 381 (20), 380 (100).

h) Spectral data for Example 198:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.40 (1H, d,  $J = 4.0$  Hz), 7.58 (1H, d,  $J = 1.8$  Hz), 7.55 (1H, d,  $J = 8.4$  Hz), 7.41 (1H, dd,  $J = 8.4, 1.8$  Hz), 6.67 (1H, d,  $J = 4.0$  Hz), 3.79 (2H, d,  $J = 7.3$  Hz), 3.38  
20 (3H, s), 3.37 (1H, m), 2.82 (2H, q,  $J = 7.3$  Hz), 1.47 (3H, d,  $J = 7.0$  Hz), 1.25 (3H, t,  $J = 7.3$  Hz). Mass Spectrum (AP-CI): m/e 364 (100), 366 (65), 368 (12.5).

High resolution mass spectrum: for  $\text{C}_{18}\text{H}_{20}\text{Cl}_2\text{N}_3\text{O}$  m/e calculated: 364.0984, observed 364.0988.

i) Spectral data for Example 270: TLC  $R_f$  0.19 (5:95 ethyl acetate-hexane).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.42 (1H, d,  $J = 4.4$  Hz), 7.84 (1H, br s), 7.76 (1H, d,  $J = 8.1$  Hz), 7.69 (1H, d,  $J = 8.1$  Hz), 6.68 (1H, d,  $J = 4.4$  Hz), 2.79  
30 (2H, q,  $J = 7.7$  Hz), 2.78-2.68 (1H, m), 2.02-1.80 (4H, m), 1.25 (3H, t,  $J = 7.7$  Hz), 0.84 (6H, t,  $J = 7.5$  Hz).

91

MS (NH<sub>3</sub>-CI): m/e 399 (7), 398 (33), 397 (25), 396 (100).  
Analysis calc'd for C<sub>20</sub>H<sub>21</sub>ClF<sub>3</sub>N<sub>3</sub>: C, 60.68; H, 5.36; N, 10.62; found: C, 60.66; H, 5.15; N, 10.48.

5

Additional Examples of Compounds Made According to the  
Above-Described Synthetic Scheme and Examples

7-(2,4-dichloro-5-fluorophenyl)-2-ethyl-3-(2-pentyl)-  
pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethyl-6-methyl-3-(2-pentyl)-  
pyrazolo[1,5-a]pyrimidine

7-(2-chloro-4-methoxyphenyl)-2-ethyl-3-(2-  
pentyl)pyrazolo[1,5-a]pyrimidine

2-ethyl-3-(2-pentyl)-7-(2,4,6-trimethylphenyl)-  
pyrazolo[1,5-a]pyrimidine

2-ethyl-3-(2-pentyl)-7-(2,4,6-trimethoxyphenyl)-  
pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethyl-3-(2-pentyl)pyrazolo[1,5-  
a]pyrimidine

7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidine-3-  
carboxaldehyde

7-(2,4-dichlorophenyl)-2-ethyl-3-(1-hydroxyethyl)-  
pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-3-(1-ethoxyethyl)-2-ethyl-  
pyrazolo[1,5-a]pyrimidine

7-(2,4-dichlorophenyl)-3-(1-ethoxyethyl)-2-  
ethylpyrazolo[1,5-a]pyrimidine

2-ethyl-7-(2-methyl-4-methoxyphenyl)-3-(3-pentyl)-  
pyrazolo[1,5-a]pyrimidine

2-ethyl-7-(2-methyl-4-methoxyphenyl)-3-(2-pentyl)-  
pyrazolo[1,5-a]pyrimidine

7-(2,4-dimethylphenyl)-2-ethyl-3-(2-pentyl)-pyrazolo[1,5-

a]pyrimidine  
7-(2,4-dichlorophenyl)-2-ethyl-5-methylthio-3-(2-pentyl)-  
pyrazolo[1,5-a]pyrimidine  
7-(2,4-dichlorophenyl)-2-ethyl-3-(6-methyl-5-hepten-2-yl)-  
pyrazolo[1,5-a]pyrimidine  
7-(2,4-dichlorophenyl)-2-ethyl-3-(1-hydroxy-4-pentyl)-  
pyrazolo[1,5-a]pyrimidine  
7-(4-difluoromethoxy-2-methyl)-2-ethyl-3-(3-  
pentyl)pyrazolo[1,5-a]pyrimidine  
7-(4-difluoromethoxy-2-methyl)-2-ethyl-3-(2-  
pentyl)pyrazolo[1,5-a]pyrimidine  
7-(2-chloro-4-difluoromethoxyphenyl)-2-ethyl-3-(3-  
pentyl)pyrazolo[1,5-a]pyrimidine  
7-(2-chloro-4-difluoromethoxyphenyl)-2-ethyl-3-(2-  
pentyl)pyrazolo[1,5-a]pyrimidine  
7-(2,4-dimethylphenyl)-2-ethyl-3-(3-pentyl)pyrazolo[1,5-  
a]pyrimidine  
4-(7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-  
a]pyrimidinyl)pentanoic acid  
4-(7-(2,4-dichlorophenyl)-2-ethylpyrazolo[1,5-  
a]pyrimidinyl)-N-methylpentanamide  
3-(5-(benzoxazol-2-ylthio)-2-pentyl)-7-(2,4-  
dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidine  
3-(5-(benzoxazolidinethione-3-yl)-2-pentyl)-7-(2,4-  
dichlorophenyl)-2-ethylpyrazolo[1,5-a]pyrimidine  
7-(2,4-dichlorophenyl)-2-ethyl-3-(1-hydroxy-2-propyl)-  
pyrazolo[1,5-a]pyrimidine  
7-(2,4-dichlorophenyl)-3-(1-ethoxy-2-propyl)-2-ethyl-  
pyrazolo[1,5-a]pyrimidine  
3-(1-acetoxy-2-propyl)-7-(2,4-dichlorophenyl)-2-  
ethylpyrazolo[1,5-a]pyrimidine  
3-(1-acetoxy-2-butyl)-7-(2,4-dichlorophenyl)-2-  
ethylpyrazolo[1,5-a]pyrimidine

9

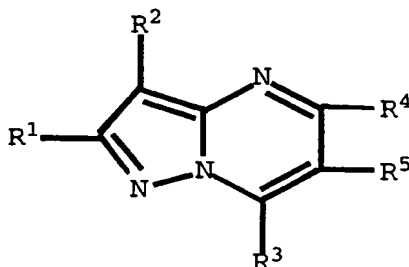
7-(2,4-dichlorophenyl)-2-ethyl-3-(1-hydroxy-3-butyl)pyrazolo[1,5-a]pyrimidine  
7-(2,4-dichlorophenyl)-2-ethyl-3-(1-methoxy-3-butyl)pyrazolo[1,5-a]pyrimidine  
7-(2,4-dichlorophenyl)-2-ethyl-3-(3-heptyl)-pyrazolo[1,5-a]pyrimidine  
7-(2,4-dichlorophenyl)-2-ethyl-3-(3-heptyl)-6-methyl-pyrazolo[1,5-a]pyrimidine  
2-ethyl-3-(3-heptyl)-7-(2,4,6-trimethylphenyl)-pyrazolo[1,5-a]pyrimidine  
7-(2,4-dichlorophenyl)-2-ethyl-3-(3-pentyl)-pyrazolo[1,5-a]pyrimidine  
7-(2,4-dichlorophenyl)-2-ethyl-3-(3-pentyl)-6-methyl-pyrazolo[1,5-a]pyrimidine  
2-ethyl-3-(3-pentyl)-7-(2,4,6-trimethylphenyl)-pyrazolo[1,5-a]pyrimidine  
2-ethyl-3-(3-pentyl)-7-(2,4,6-trimethoxyphenyl)-pyrazolo[1,5-a]pyrimidine

Although the present invention has been described  
5 and exemplified in terms of certain preferred  
embodiments, other embodiments will be apparent to  
those skilled in the art. The invention is, therefore,  
not limited to the particular embodiments described and  
exemplified, but is capable of modification or  
10 variation without departing from the spirit of the  
invention, the full scope of which is delineated by the  
appended claims.

94

WHAT IS CLAIMED IS:

1. A compound of formula I:



(I)

5

or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

$R^1$  is selected from the group consisting of

10  $C_{1-6}$  alkyl,

$C_{2-10}$  alkenyl,

$C_{2-10}$  alkynyl,

$C_{3-6}$  cycloalkyl,

$C_{1-6}$  alkyloxy,

15  $C_{1-6}$  alkylS(O)<sub>n</sub>,

$-NR^{1a}R^{1b}$  wherein  $R^{1a}$  and  $R^{1b}$  are independently selected from

H,  $C_{1-4}$  alkyl,  $-C(O)C_{1-4}$ alkyl,

$-C(O)NR^{1a}R^{1b}$ ,

$-O-C(O)C_{1-4}$ alkyl,

20  $-XR^{1c}$  wherein  $R^{1c}$  is selected from H or  $-C_{1-4}$  alkylaryl;

X is selected from O or S(O)<sub>n</sub>,

wherein  $R^1$  is substituted with 0-6 substituents selected from halogen,  $C_{1-4}$  alkyl,  $C_{1-6}$  alkyloxy,  $C_{1-4}$  haloalkyl,  $-NR^{1a}R^{1b}$ ,  $-XR^{1c}$ ;

25

$R^2$  is selected from the group consisting of

$C_{1-10}$  alkyl,

$C_{2-10}$  alkenyl,



95

- $C_{2-10}$  alkynyl,  
 $C_{3-8}$  cycloalkyl,  
 $C_{3-6}$  cycloalkyl  $C_{1-6}$  alkyl,  
 $C_{1-10}$  alkyloxy,  
5  $C_{1-10}$  alkyloxy $C_{1-10}$  alkyl,  
 $-SO_2-C_{1-10}$ alkyl  
 $-SO_2R^{2a}$  wherein  $R^{2a}$  is aryl,  
 $-SO_2R^{2b}$  wherein  $R^{2b}$  is heteroaryl,  
 $-NR^{2c}R^{2d}$  wherein  $R^{2c}$  and  $R^{2d}$  are independently selected from  
10 H,  $C_{1-8}$  alkyl,  $S(O)_n C_{1-4}$ alkyl,  $C(O)NR^{2c}R^{2d}$ ,  $CO_2C_{1-4}$ alkyl,  
 $C_{3-8}$  cycloalkyl,  $C_{1-6}$  alkyloxy $C_{1-6}$  alkyl,  $-C(O)C_{1-4}$ alkyl  
or  $R^{2c}$  and  $R^{2d}$  may join to form a heterocyclic ring  
having 0-3 heteroatoms selected from O, N or S,  
15 - halogen,  
-CN,  
 $-C(O)L$  wherein L is selected from  $NR^{2c}R^{2d}$ ,  $C_{1-6}$  alkyl, H,  
 $-OC_{1-6}$  alkyl,  $O(CH_2)_m OC_{1-6}$ alkyl,  $O(CH_2)_m NR^{2c}R^{2d}$ , -OH, aryl,  
heteroaryl or  $C(O)OC_{1-6}$  alkyl wherein m is 1-3;  
20  
n is 0, 1 or 2;  
 $R^2$  is substituted with 0-3 substituents independently  
25 selected from  $R'$ ,  $R''$ ,  $R'''$  wherein  $R'$ ,  $R''$  and  $R'''$  are  
independently selected from  $C_{1-6}$  alkyl,  $C_{3-7}$  cycloalkyl,  
hydroxy $C_{1-6}$  alkyl,  $C_{1-6}$  alkyloxy $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{1-6}$   
alkyloxy, hydroxy; or  
30  $R^2$  is substituted with 0-3 substituents independently  
selected from  
halogen,  
-CN,

- $C_{16}$
- S(O)<sub>n</sub>R<sup>2e</sup> wherein R<sup>2e</sup> is selected from C<sub>1-4</sub> alkyl, C<sub>1-4</sub> haloalkyl, C<sub>1-4</sub> alkyloxy C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl;
- 5 -COR<sup>2f</sup> wherein R<sup>2f</sup> is selected from H, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> haloalkyl, C<sub>1-4</sub> alkyloxy C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl, and C<sub>3-6</sub> cycloalkylC<sub>1-4</sub> alkyl;
- CO<sub>2</sub>R<sup>2f</sup>,
- NR<sup>2g</sup>COR<sup>2f</sup> wherein R<sup>2g</sup> is selected from H, C<sub>1-6</sub> alkyl, C<sub>3-7</sub> c-alkyl, C<sub>3-6</sub> cycloalkyl C<sub>1-6</sub> alkyl;
- 10 -N(COR<sup>2f</sup>)<sub>2</sub>,
- NR<sup>2g</sup>CONR<sup>2f</sup>R<sup>2h</sup>, wherein R<sup>2h</sup> is selected from H, C<sub>1-6</sub> alkyl, C<sub>1-4</sub> haloalkyl, C<sub>1-4</sub> alkoxy C<sub>1-4</sub> alkyl, C<sub>3-6</sub> cycloalkyl and C<sub>3-6</sub> cycloalkylC<sub>1-6</sub> alkyl;
- 15 -NR<sup>2g</sup>CO<sub>2</sub>R<sup>2e</sup>,
- CONR<sup>2g</sup>R<sup>2h</sup>,
- 1-morpholinyl,
- 1-piperidinyl,
- 20 1-piperazinyl,
- and
- C<sub>3-8</sub> cycloalkyl wherein 0-1 carbon atoms in the C<sub>4-8</sub> cycloalkyl is replaced by a group selected from
- O-, -S(O)<sub>n</sub>-, -NR<sup>2g</sup>-, -NCO<sub>2</sub>R<sup>2e</sup>, -NCOR<sup>2e</sup>,
- 25 and -NSO<sub>2</sub>R<sup>2e</sup>; and wherein N<sub>4</sub> in
- 1-piperazinyl is substituted with 0-1 substituents selected from R<sup>2g</sup>, CO<sub>2</sub>R<sup>2e</sup>, COR<sup>2e</sup> and SO<sub>2</sub>R<sup>2e</sup>; or
- 30 the group R<sup>2i</sup>, R<sup>2j</sup>, R<sup>2k</sup>, C<sub>1-6</sub> alkyl, C<sub>2-8</sub> alkenyl, C<sub>2-8</sub> alkynyl, Br, Cl, F, I, C<sub>1-4</sub> haloalkyl, -OR<sup>2g</sup>, -NR<sup>2g</sup>R<sup>2h</sup>, -C<sub>1-6</sub> alkylOR<sup>2g</sup>, and C<sub>3-8</sub> cycloalkyl which is substituted with 0-1 R<sup>2i</sup> and in which 0-1 carbons of C<sub>4-8</sub>

47

- cycloalkyl is replaced by -O-, wherein  $R^{2i}$  is selected from aryl wherein aryl includes phenyl, naphthyl, indanyl and indenyl, each  $R^{2i}$  being substituted with 0-1  $OR^{2m}$  and 0-5
- 5 substituents independently selected from the group  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl, Br, Cl, F, I,  $C_{1-4}$  haloalkyl, -CN, nitro, -SH,  $-S(O)_nR^{2n}$ ,  $-COR^{2m}$ ,  $-OC(O)R^{2n}$ ,  $-NR^{2g}COR^{2m}$ ,  $-N(COR^{2m})_2$ ,  $-NR^{2g}CONR^{2o}R^{2p}$ ,  $-NR^{2g}CO_2R^{2n}$ ,  $-NR^{2o}R^{2p}$  and  $-CONR^{2o}R^{2p}$ ;
- 10  $R^{2j}$  is selected from heteroaryl wherein heteroaryl includes pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl,
- 15 benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, 2,3-dihydrobenzothienyl-s-oxide, 2,3-dihydro-benzothienyl-S-dioxide, indolinyl, benzoxazolin-2-onyl, benzodioxolanyl
- 20 and benzodioxane, each heteroaryl being substituted on 0-4 carbon atoms with a substituent independently selected from the group  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl, Br, Cl, F, I,  $C_{1-4}$  haloalkyl, -CN, nitro,  $OR^{2m}$ , -SH,  $-S(O)_nR^{2n}$ ,  $-COR^{2m}$ ,  $-OC(O)R^{2n}$ ,  $-NR^{2g}COR^{2m}$ ,  $-N(COR^{2m})_2$ ,  $-NR^{2g}CONR^{2o}R^{2p}$ ,  $-NR^{2g}CO_2R^{2n}$ ,  $-NR^{2o}R^{2p}$  and  $-CONR^{2o}R^{2p}$  and each heteroaryl being substituted
- 25 on any nitrogen atom with 0-1 substituents selected from the group  $R^{2o}$ ,  $CO_2R^{2e}$ ,  $COR^{2e}$  and  $SO_2R^{2e}$ ;
- $R^{2k}$  is heterocyclyl which is a saturated or partially
- 30 saturated heteroaryl as defined for  $R^{2j}$ , each heterocyclyl being substituted on 0-4 carbon atoms with a substituent independently selected from the group  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl, Br, Cl, F, I,  $C_{1-4}$  haloalkyl, -CN, nitro,  $-OR^{2m}$ ,

98

-SH,  $-S(O)_nR^{2h}$ ,  $-COR^{2m}$ ,  $-OC(O)R^{2h}$ ,  $-NR^{2q}COR^{2m}$ ,  $-N(COR^{2m})_2$ ,  
 $-NR^{2q}CONR^{2o}R^{2p}$ ,  $NR^{2q}CO_2R^{2h}$ ,  $-NR^{2o}R^{2p}$  and  $-CONR^{2o}R^{2p}$  and each  
heterocyclyl being substituted on any nitrogen atom with  
0-1 substituents selected from the group  $R^{2f}$ ,  $CO_2R^{2e}$ ,  $COR^{2e}$   
5 and  $SO_2R^{2e}$ ;

wherein

$R^{21}$  is H,  $C_{1-4}$  alkyl,  $C_{3-6}$  cycloalkyl- $C_{1-4}$  alkyl and  $C_{3-8}$   
10 cycloalkyl;

$R^{2m}$  is H,  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl  $C_{1-6}$  alkyl,  $C_{1-2}$   
alkyloxy  $C_{1-2}$  alkyl,  $C_{1-4}$  haloalkyl,  $R^{2a}S(O)_n-C_{1-4}$  alkyl  
and  $R^{2x}R^{2s}N-C_{2-4}$  alkyl;  
15

$R^{2n}$  is H,  $C_{1-6}$  alkyl,  $C_{3-10}$  cycloalkyl,  $C_{3-6}$  cycloalkyl-  
 $C_{1-6}$  alkyl,  $C_{1-2}$  alkyloxy  $C_{1-2}$  alkyl, and  $C_{1-4}$  haloalkyl;

$R^{2o}$  and  $R^{2p}$  are independently selected at each occurrence  
20 from H,  $C_{1-6}$  alkyl,  $C_{3-10}$  cycloalkyl,  $C_{3-6}$  cycloalkyl  $C_{1-6}$  alkyl  
and  $C_{1-4}$  haloalkyl;

$R^{2a}$  is selected from  $C_{1-6}$  alkyl,  $C_{1-4}$  haloalkyl,  $C_{1-4}$  alkoxy-  
 $C_{1-4}$  alkyl,  $C_{3-6}$  cycloalkyl,  $C_{3-6}$  cycloalkyl-  $C_{1-6}$  alkyl, aryl,  
25 aryl( $C_{1-4}$  alkyl), heteroaryl and heteroaryl ( $C_{1-4}$  alkyl)-  
and benzyl, each benzyl being substituted on the aryl  
moiety with 0-1 substituents selected from the group  $C_{1-4}$   
alkyl, Br, Cl, F, I,  $C_{1-4}$  haloalkyl, nitro,  $C_{1-4}$  alkoxy  $C_{1-4}$   
haloalkoxy, and dimethylamino;

30

$R^{2x}R^{2s}$  taken together with the N form 1-pyrrolidinyl, 1-  
morpholinyl, 1-piperidinyl or 1-piperazinyl wherein  $N_4$  in

99

1-piperiazinyl is substituted with 0-1 substituents selected from the group  $R^{2t}$ ,  $CO_2R^{2q}$ ,  $COR^{2q}$  and  $SO_2R^{2q}$ ;

$R^{2t}$  is selected from H,  $C_{1-4}$  alkyl,  $C_{1-4}$  haloalkyl,  $C_{1-4}$  alkoxy  
5  $-C_{1-4}$  alkyl,  $C_{3-6}$  cycloalkyl,  $C_{3-6}$  cycloalkyl -  $C_{1-6}$  alkyl, aryl, aryl ( $C_{1-4}$  alkyl)-, heteroaryl and heteroaryl ( $C_{1-4}$  alkyl);

$R^3$  is selected from an aryl or heteroaryl group attached  
10 through an unsaturated carbon atom;

aryl is selected from phenyl, naphthyl, indanyl and indenyl, each aryl being substituted with 0-5 substituents independently selected at each occurrence  
15 from  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl, methylenedioxy,  $C_{1-4}$  alkyloxy- $C_{1-4}$  alkyloxy,  $-OR^{2m}$ , Br, Cl, F, I,  $C_{1-4}$  haloalkyl,  $-CN$ ,  $-NO_2$ ,  $-SH$ ,  $-S(O)_nR^{2n}$ ,  $-COR^{2m}$ ,  $-CO_2R^{2m}$ ,  $-OC(O)R^{2n}$ ,  $-NR^{2q}COR^{2m}$ ,  $-N(COR^{2m})_2$ ,  $-NR^{2q}CONR^{2o}R^{2p}$ ,  $-NR^{2q}CO_2R^{2h}$ ,  $-NR^{2o}R^{2p}$  and  $CONR^{2o}R^{2p}$  and up to 1 phenyl, each phenyl substituent being  
20 substituted with 0-4 substituents selected from the group  $C_{1-3}$  alkyl,  $C_{1-3}$  alkoxy, Br, Cl, F, I,  $-CN$ , dimethylamino,  $CF_3$ ,  $C_2F_5$ ,  $OCF_3$ ,  $SO_2Me$  and acetyl;

heteroaryl is selected from the group pyridyl, pyrimidyl,  
25 triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzo-furanyl, 2,3-dihydrobenzothienyl, 2,3-dihydro-benzothienyl-S-oxide, 2,3-dihydrobenzothienyl-s-dioxide, indolinyl, benzoxazolin-2-on-yl, benzodioxolanyl and benzodioxane, each heteroaryl being substituted at 0-4 carbon atoms with a substituent independently selected at  
30

(b)

each occurrence from the group  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl, Br, F, I,  $C_{1-4}$  haloalkyl,  $-CN$ ,  $NR^{2g}R^{2h}$ , nitro,  $-OR^{2m}$ ,  $-SH$ ,  $-S(O)_nR^{2n}$ ,  $COR^{2m}$ ,  $-CO_2R^{2m}$ ,  $-OC(O)R^{2n}$ ,  $-NR^{2g}COR^{2m}$ ,  $-N(COR^{2m})_2$ ,  $-NR^{2g}CONR^{2o}R^{2p}$  and each heteroaryl being substituted at any  
 5 nitrogen atom with 0-1 substituents selected from the group  $R^{2g}$ ,  $CO_2R^{3a}$ ,  $COR^{3a}$  and  $SO_2R^{3a}$  wherein,

$R^{3a}$  is selected from the group  $C_{1-6}$  alkyl,  $C_{1-4}$  cycloalkyl- $C_{1-6}$  alkyl and benzyl, each benzyl being substituted on the  
 10 aryl moiety with 0-1 substituents selected from the group  $C_{1-4}$  alkyl, Br, Cl, F, I,  $C_{1-4}$  haloalkyl, nitro,  $C_{1-4}$  alkoxy,  $C_{1-4}$  haloalkoxy, and dimethylamino;

$R^4$  and  $R^5$  are independently selected at each occurrence  
 15 from H, Br, Cl, F, I,  $-CN$ ,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{3-8}$  cycloalkyl,  $C_{1-6}$  alkyloxy,  $C_{1-6}$  alkylthio,  $C_{1-6}$  alkylsulfinyl,  $C_{1-6}$  alkylsulfonyl, amino,  $C_{1-4}$  alkylamino,  $(C_{1-4}$  alkyl)<sub>2</sub> amino and phenyl, each phenyl is substituted with 0-3 groups selected from the group consisting of  $C_{1-7}$   
 20 alkyl,  $C_{3-8}$  cycloalkyl, Br, Cl, F, I,  $-C(O)H$ ,  $C_{1-4}$  haloalkyl, nitro,  $C_{1-4}$  alkoxy,  $C_{1-4}$  haloalkoxy,  $C_{1-4}$  alkylthio,  $C_{1-4}$  alkylsulfinyl,  $C_{1-4}$  alkylsulfonyl,  $C_{1-6}$  alkylamino and  $(C_{1-4}$  alkyl)<sub>2</sub> amino and wherein  $R^4$  and  $R^5$  non-phenyl groups may be substituted with 0-5  
 25 substituents selected from OH, halogen,  $-C(O)H$ ,  $-OC_{1-6}-$  alkyl and  $C_{1-6}$  haloalkyl,  $C_{1-6}$  alkyl,  $C_{3-7}$  c-alkyl,  $C_{1-6}$  alkyl(OH)<sub>n</sub>CO<sub>2</sub>R wherein R is H or  $C_{1-6}$  alkyl,  $C_{1-6}$  alkyl(OH)<sub>n</sub>, wherein n is 0-3 or  $R^4$  and  $R^5$  may join together to form a  $C_{3-6}$  alkylene chain; with the proviso that the compounds of  
 30 Formula I with  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  as specifically defined below are excluded:

101

- (a) a compound of formula I wherein  $R^1$  is unsubstituted, unbranched (linear)  $C_{1-3}$  alkyl and  $R^2$  is  $-C(O)-Ph$ ;
- (b) a compound of formula I, wherein  $R^5$  is H or  $C_{1-3}$  alkyl and  $R^3$  is pyridyl, pyridyl-N-oxide, thien-3-yl or furan-3-yl or  $C_{1-3}$  alkyl substituted versions thereof and  $R^1$  is carboamoyl or unsubstituted, unbranched  $C_{1-3}$  alkyl,  $R^2$  is F, Cl, Br, formyl, carboxyl, CN, hydroxymethyl, unsubstituted, unbranched  $C_{1-3}$  alkyl,  $-C(O)R$ ,  $-C(O)OR$ ,  $-CH_2OR$ ,  $-C(O)O(CH_2)_2OR$ ,  $-C(O)O(CH_2)_2NHR$ , or  $-C(O)O(CH_2)_2NR^2$  wherein R is  $C_{1-3}$  alkyl;
- (c) a compound of formula I, wherein  $R^1$  is unsubstituted, unbranched  $C_{1-3}$  alkyl and  $R^2$  is halogen, CN or  $-C(O)R$  wherein R is H,  $C_{1-3}$  alkyl or  $C_{1-4}$  alkoxy,  $R^3$  is Ph substituted with  $NR^{2q}C(O)R^{2m}$ ;
- (d) a compound of formula I,  $R^2$  is CN, halogen,  $CO_2R$  with R equal to  $C_{1-3}$  alkyl, unsubstituted, unbranched  $C_{1-3}$  alkyl,  $C_{1-3}$  haloalkyl or  $CONH_2$  and  $R^1$  is equal to OR, SR wherein R is  $C_{1-3}$  alkyl,  $C_{1-4}$  haloalkyl or  $C_{3-4}$  halocycloalkyl, and  $R^3$  is phenyl or substituted phenyl;
- (e) a compound of formula I, wherein  $R^5$  is H or  $C_{1-3}$  alkyl;  $R^3$  is phenyl, ortho-trifluoromethylphenyl, meta-trifluorophenyl or meta-methoxyphenyl;  $R^1$  is carbamoyl or unsubstituted, unbranched  $C_{1-3}$  alkyl;  $R^2$  is halogen, formyl, carboxyl, cyano, hydroxymethyl, unsubstituted, unbranched  $C_{1-3}$  alkyl,  $-C(O)R$ ,  $-C(O)OR$ ,  $CH_2OR$ ,  $-C(O)O(CH_2)_2OR$ ,  $-C(O)O(CH_2)_2NHR$  or  $-C(O)O(CH_2)_2NR^2$  wherein R is  $C_{1-3}$  alkyl;
- (g) in a compound of formula I,  $R^2$  is CN,  $R^1$  is methyl,  $R^4$  and  $R^5$  are H,  $R^3$  is phenyl substituted with imidazo (or 2-methylimidazo) through the imidazo nitrogen atom;
- (h) in a compound of formula I,  $R^2$  is CN,  $R^1$  is  $SCH_3$ ,  $R^3$  is para-chlorophenyl,  $R^4$  is  $SCH_3$  and  $R^5$  is H;

162

- (i) in a compound of formula I,  $R^2$  is CN,  $R^1$  is  $\text{SCH}_3$ ,  $R^3$  is pyrid-4-yl,  $R^4$  is  $\text{SCH}_3$  and  $R^5$  is H ;
- (j) in a compound of formula I,  $R^2$  is CN,  $R^1$  is  $\text{SCH}_3$ ,  $R^3$  is Ph,  $R^4$  is  $\text{SCH}_3$  and  $R^5$  is H ;
- 5 (k) in a compound of formula I,  $R^2$  is  $\text{C(O)NH}_2$ ,  $R^1$  is  $\text{SCH}_3$ ,  $R^3$  is pyrid-3-yl,  $R^4$  is  $\text{SCH}_3$  and  $R^5$  is H ;
- (l) in a compound of formula I,  $R^2$  is  $\text{C(O)NH}_2$ ,  $R^1$  is  $\text{SCH}_3$ ,  $R^3$  is Ph,  $R^4$  is  $\text{SCH}_3$  (or Ph) and  $R^5$  is H ;
- (m) in a compound of formula I,  $R^2$  is  $\text{C(O)OEt}$ ,  $R^1$  is  $\text{SCH}_3$ ,  
10  $R^3$  is Ph,  $R^4$  is  $\text{SCH}_3$  (or Ph) and  $R^5$  is H ;
- (n) in a compound of formula I,  $R^1$  is  $\text{N(C(O)CH}_3)_2$ ,  $R^2$  is  $\text{CH}_2\text{Ph(p-Me, p-Cl)}$ ,  $R^3$  is Ph (p-ClPh),  $R^4$  is  $\text{SCH}_3$  and  $R^5$  is H;
- (o) in a compound of formula I,  $R^1$  is  $\text{N(C(O)CH}_3)_2$ ,  $R^2$  is  
15  $\text{CH}_2\text{Ph(p-OMe)}$ ,  $R^3$  is p-ClPh,  $R^4$  is  $\text{SCH}_3$  and  $R^5$  is H ;
- (p) in a compound of formula I,  $R^2$  is CN,  $R^1$  is  $\text{CH}_3$ ,  $R^3$  is Ph,  $R^4$  is H and  $R^5$  is H;
- (q) in a compound of formula I,  $R^2$  is  $\text{C(O)NH}_2$ ,  $R^1$  is  $\text{CH}_3$ ,  $R^3$  is Ph,  $R^4$  is  $\text{CH}_3$  and  $R^5$  is H;
- 20 (s) in a compound of formula I,  $R^2$  is  $\text{C(O)NH}_2$ ,  $R^1$  is  $\text{CH}_3$ ,  $R^3$  is pyrid-4-yl,  $R^4$  and  $R^5$  are H;
- (t) in a compound of formula I,  $R^2$  is  $\text{C(O)NH}_2$ ,  $R^1$  is  $\text{CH}_3$ ,  $R^3$  is m- $\text{CF}_3\text{Ph}$ ,  $R^4$  and  $R^5$  are H ;
- (u) in a compound of formula I,  $R^2$  is CN,  $R^1$  is  $\text{CH}_3$ ,  $R^3$  is  
25 Ph,  $R^4$  is  $\text{CH}_3$  and  $R^5$  is H ;
- (v) in a compound of formula I,  $R^2$  is CN,  $R^1$  is  $\text{CH}_3$ ,  $R^3$  is pyrid-4-yl,  $R^4$  and  $R^5$  are H ;
- (x) in a compound of formula I,  $R^2$  is  $\text{CH}_3$ ,  $R^1$  is  $\text{CH}_3$ ,  $R^3$  is p-F-Ph,  $R^4$  is c-propyl and  $R^5$  is  $\text{CH=CH-}$   
30  $\text{CH(OH)CH}_2\text{CH(OH)CH}_2\text{C(O)O-iPr}$ ;
- (y) in a compound of formula I,  $R^2$  is  $\text{CH}_3$ ,  $R^1$  is  $\text{CH}_3$ ,  $R^3$  is p-F-Ph,  $R^4$  is c-propyl and  $R^5$  is  $\text{CH=CH-}$   
 $\text{CH(OH)CH}_2\text{CH(OH)CH}_2\text{C(O)O-nPr}$ ;



103

- (z) in a compound of formula I,  $R^2$  is  $CH_3$ ,  $R^1$  is  $CH_3$ ,  $R^3$  is p-F-Ph,  $R^4$  is c-propyl and  $R^5$  is  $CH=CH-CH(OH)CH_2CH(OH)CH_2C(O)OMe$ ;
- 5 (aa) in a compound of formula I,  $R^2$  is  $CH_3$ ,  $R^1$  is  $CH_3$ ,  $R^3$  is p-F-Ph,  $R^4$  is c-propyl and  $R^5$  is  $CH=CH-CH(OH)CH_2CH(OH)CH_2C(O)OH$ ;
- (bb) in a compound of formula I,  $R^2$  is  $CH_3$ ,  $R^1$  is  $CH_3$ ,  $R^3$  is p-F-Ph,  $R^4$  is c-propyl and  $R^5$  is  $-CH_2OH$ ;
- 10 (cc) in a compound of formula I,  $R^2$  is  $CH_3$ ,  $R^1$  is  $CH_3$ ,  $R^3$  is p-F-Ph,  $R^4$  is c-propyl and  $R^5$  is  $-C(O)H$ ;
- (dd) in a compound of formula I,  $R^2$  is  $CH_3$ ,  $R^1$  is  $CH_3$ ,  $R^3$  is p-F-Ph,  $R^4$  is c-propyl and  $R^5$  is  $-CH=CH-C(O)H$ ;
- (ee) in a compound of formula I,  $R^2$  is  $CH_3$ ,  $R^1$  is  $CH_3$ ,  $R^3$  is p-F-Ph,  $R^4$  is c-propyl and  $R^5$  is  $CH=CH-CH(OH)CH_2CH(OH)CH_2C(O)OEt$ ;
- 15 (ff) in a compound of formula I,  $R^2$  is  $CH_3$ ,  $R^1$  is  $CH_3$ ,  $R^3$  is p-F-Ph,  $R^4$  is c-propyl and  $R^5$  is  $CH=CH-CH(OH)CH_2CH(OH)CH_2C(O)O^-Na^+$ ;
- (gg) in a compound of formula I,  $R^2$  is CN,  $R^1$  is  $CF_3$ ,  $R^3$  is m-Cl-Ph,  $R^4$  is  $CH_3$  and  $R^5$  is H;
- 20 (hh) in a compound of formula I,  $R^2$  is CN,  $R^1$  is  $CF_3$ ,  $R^3$  is m- $CF_3$ -Ph,  $R^4$  is  $CH_3$  and  $R^5$  is H;
- (ii) in a compound of formula I,  $R^2$  is CN,  $R^1$  is  $CF_3$ ,  $R^3$  is Ph,  $R^4$  is  $CH_3$  and  $R^5$  is H;
- 25 (nn) in a compound of formula I,  $R^2$  is  $-C(O)NH_2$ ,  $R^1$  is Me,  $R^3$  is Ph,  $R^4$  is H and  $R^5$  is Me;
- (oo) in a compound of formula I,  $R^2$  is CN,  $R^1$  is Me,  $R^3$  is Ph,  $R^4$  is H and  $R^5$  is Me;
- (pp) in a compound of formula I,  $R^2$  is CN,  $R^1$  is Me,  $R^3$  is
- 30 o-Cl,m-Cl-Ph,  $R^4$  is H and  $R^5$  is H;
- (qq) in a compound of formula I,  $R^2$  is  $C(O)NH_2$ ,  $R^1$  is  $CH_3$ ,  $R^3$  is Ph,  $R^4$  and  $R^5$  are H ;

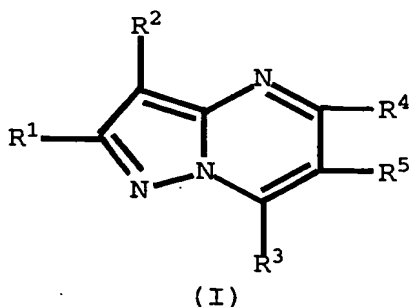
104

- (rr) in a compound of formula I,  $R^2$  is  $C(O)NH_2$ ,  $R^1$  is  $CH_3$ ,  $R^3$  is  $O-CL, m-Cl-Ph$ ,  $R^4$  and  $R^5$  are H ;
- (ss) in a compound of formula I,  $R^2$  is  $C(O)OMe$ ,  $R^1$  is  $-SCH_2-Ph$ ,  $R^3$  is Ph,  $R^4$  is Me and  $R^5$  is H ;
- 5 (tt) in a compound of formula I,  $R^2$  is  $C(O)OMe$ ,  $R^1$  is  $-SCH_2-Ph$ ,  $R^3$  is Ph,  $R^4$  is H and  $R^5$  is H ;
- (uu) in a compound of formula I,  $R^2$  is  $C(O)Ph$ ,  $R^1$  is Me,  $R^3$  is pyrid-4-yl,  $R^4$  and  $R^5$  are H ;
- (vv) in a compound of formula I,  $R^2$  is  $C(O)Ph$ ,  $R^1$  is Me,  $R^3$  is  $m-CF_3-Ph$ ,  $R^4$  and  $R^5$  are H ;
- 10 (ww) in a compound of formula I,  $R^2$  is  $C(O)Ph$ ,  $R^1$  is Me,  $R^3$  is pyrid-3-yl,  $R^4$  and  $R^5$  are H
- (xx) in a compound of formula I,  $R^2$  is CN,  $R^1$  is  $SCH_3$ ,  $R^3$  is Ph,  $R^4$  is Ph and  $R^5$  is H ;
- 15 (yy) in a compound of formula I,  $R^2$  is CN,  $R^1$  is  $SCH_3$ ,  $R^3$  is Ph,  $R^4$  is Ph and  $R^5$  is H ;
- (zz) in a compound of formula I,  $R^2$  is Cl,  $R^1$  is Et,  $R^3$  is pyrid-3-yl,  $R^4$  and  $R^5$  are H ;
- (aaa) in a compound of formula I,  $R^2$  is  $CO_2H$ ,  $R^1$  is Et,  $R^3$  is pyrid-3-yl,  $R^4$  and  $R^5$  are H ;
- 20 (bbb) in a compound of formula I,  $R^2$  is  $CO_2H$ ,  $R^1$  is  $CH_3$ ,  $R^3$  is pyrid-3-yl,  $R^4$  and  $R^5$  are H and H Cl salt ;
- (ccc) in a compound of formula I,  $R^2$  is  $C(O)OEt$ ,  $R^1$  is  $CH_3$ ,  $R^3$  is pyrid-3-yl,  $R^4$  and  $R^5$  are H ;
- 25 (ddd) in a compound of formula I,  $R^2$  is CN,  $R^1$  is  $CH_3$ ,  $R^3$  is pyrid-3-yl,  $R^4$  is H and  $R^5$  is  $CH_3$  ;
- (eee) in a compound of formula I,  $R^2$  is CN,  $R^1$  is  $CH_3$ ,  $R^3$  is pyrid-3-yl,  $R^4$  and  $R^5$  are H ;
- (fff) in a compound of formula I,  $R^2$  is  $C(O)OEt$ ,  $R^1$  is Et,  $R^3$  is pyrid-3-yl,  $R^4$  and  $R^5$  are H ;
- 30 (ggg) in a compound of formula I,  $R^2$  is CN,  $R^1$  is Et,  $R^3$  is pyrid-3-yl,  $R^4$  and  $R^5$  are H ;

105

- (hhh) in a compound of formula I,  $R^2$  is CN,  $R^1$  is  $CH_3$ ,  $R^3$  is m- $CF_3$ -Ph,  $R^4$  and  $R^5$  are H ;
- (iii) in a compound of formula I,  $R^2$  is CN,  $R^1$  is  $CH_2CN$ ,  $R^3$  is m- $CF_3$ -Ph,  $R^4$  and  $R^5$  are H ;
- 5 (jjj) in a compound of formula I,  $R^2$  is C(O)OMe,  $R^1$  is Me,  $R^3$  is m- $CF_3$ -Ph,  $R^4$  and  $R^5$  are H ;
- (kkk) in a compound of formula I,  $R^2$  is CN,  $R^1$  is Et,  $R^3$  is m-OMe-Ph,  $R^4$  and  $R^5$  are H ;
- (lll) in a compound of formula I,  $R^2$  is C(O)OEt,  $R^1$  is Et,  $R^3$  is Ph,  $R^4$  and  $R^5$  are H ;
- 10 (mmm) in a compound of formula I,  $R^2$  is C(O)OEt,  $R^1$  is Et,  $R^3$  is m- $CF_3$ -Ph,  $R^4$  and  $R^5$  are H ;
- (nnn) in a compound of formula I,  $R^2$  is CN,  $R^1$  is Et,  $R^3$  is m- $CF_3$ -Ph,  $R^4$  is H and  $R^5$  is  $CH_3$  ;
- 15 (ooo) in a compound of formula I,  $R^2$  is CN,  $R^1$  is Et,  $R^3$  is m- $CF_3$ ,  $R^4$  and  $R^5$  are H ;
- (ppp) in a compound of formula I,  $R^2$  is CN,  $R^1$  is C(O)NH<sub>2</sub>,  $R^3$  is m- $CF_3$ -Ph,  $R^4$  and  $R^5$  are H ;
- (qqq) in a compound of formula I,  $R^2$  is CN,  $R^1$  is Et,  $R^3$  is Ph,  $R^4$  and  $R^5$  are H.
- 20

2. A compound of formula I:



25

or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

106

- $R^1$  is selected from the group consisting of
- $C_{1-6}$  alkyl,
  - $C_{2-10}$  alkenyl,
  - 5  $C_{2-10}$  alkynyl,
  - $C_{3-6}$  cycloalkyl,
  - $C_{1-6}$  alkyloxy,
  - $C_{1-6}$  alkylS(O)<sub>n</sub>,
  - NR<sup>1a</sup>R<sup>1b</sup> wherein R<sup>1a</sup> and R<sup>1b</sup> are independently selected from
  - 10 H,  $C_{1-4}$  alkyl, -C(O) $C_{1-4}$ alkyl,
  - C(O)NR<sup>1a</sup>R<sup>1b</sup>,
  - O-C(O) $C_{1-4}$ alkyl,
  - XR<sup>1c</sup> wherein R<sup>1c</sup> is selected from H or - $C_{1-4}$  alkylaryl;
  - X is selected from O or S(O)<sub>n</sub>,
  - 15 wherein R<sup>1</sup> is substituted with 0-6 substituents selected from halogen,  $C_{1-4}$  alkyl,  $C_{1-6}$  alkyloxy,  $C_{1-4}$  haloalkyl, -NR<sup>1a</sup>R<sup>1b</sup>, -XR<sup>1c</sup>;
- $R^2$  is selected from the group consisting of
- 20  $C_{1-10}$  alkyl excluding unsubstituted, unbranched  $C_{1-3}$ alkyl,
  - $C_{2-10}$  alkenyl,
  - $C_{2-10}$  alkynyl,
  - $C_{3-8}$  cycloalkyl,
  - $C_{3-6}$  cycloalkyl  $C_{1-6}$  alkyl,
  - 25  $C_{1-10}$  alkyloxy,
  - $C_{1-10}$  alkyloxy $C_{1-10}$  alkyl,
  - $C_{1-4}$  alkoxy  $C_{1-4}$  alkyl,
  - SO<sub>2</sub>- $C_{1-10}$ alkyl
  - SO<sub>2</sub>R<sup>2a</sup> wherein R<sup>2a</sup> is aryl,
  - 30 -SO<sub>2</sub>R<sup>2b</sup> wherein R<sup>2b</sup> is heteroaryl,
  - NR<sup>2c</sup>R<sup>2d</sup> wherein R<sup>2c</sup> and R<sup>2d</sup> are independently selected from
  - H,  $C_{1-8}$  alkyl, S(O)<sub>n</sub> $C_{1-4}$  alkyl, C(O)NR<sup>2c</sup>R<sup>2d</sup>, CO<sub>2</sub> $C_{1-4}$ alkyl,
  - $C_{3-8}$  cycloalkyl,  $C_{1-6}$  alkyloxy $C_{1-6}$  alkyl, -C(O) $C_{1-4}$ alkyl

107

or  $R^{2c}$  and  $R^{2d}$  may join to form a heterocyclic ring having 0-3 heteroatoms selected from O, N or S,

n is 0, 1 or 2;

5

$R^2$  is substituted with 0-3 substituents independently selected from  $R'$ ,  $R''$ ,  $R'''$  wherein  $R'$ ,  $R''$  and  $R'''$  are independently selected from  $C_{1-6}$  alkyl,  $C_{3-7}$  cycloalkyl, hydroxy $C_{1-6}$  alkyl,  $C_{1-6}$  alkyloxy $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{1-6}$  alkyloxy, hydroxy, or

10

$R^2$  is substituted with 0-3 substituents independently selected from:

-CN,

15

$-S(O)_n R^{2e}$  wherein  $R^{2e}$  is selected from  $C_{1-4}$  alkyl,  $C_{1-4}$  haloalkyl,  $C_{1-4}$  alkyloxy  $C_{1-4}$  alkyl,  $C_{3-6}$  cycloalkyl;

$-COR^{2f}$  wherein  $R^{2f}$  is selected from H,  $C_{1-4}$  alkyl,  $C_{1-4}$

haloalkyl,  $C_{1-4}$  alkyloxy  $C_{1-4}$  alkyl,  $C_{3-6}$

20

cycloalkyl, and  $C_{3-6}$  cycloalkyl $C_{1-4}$  alkyl;

$-CO_2 R^{2f}$ ,

$-NR^{2g} COR^{2f}$  wherein  $R^{2g}$  is selected from H,  $C_{1-6}$  alkyl,  $C_{3-7}$  c-alkyl,  $C_{3-6}$  cycloalkyl  $C_{1-6}$  alkyl;

25

$-N(COR^{2f})_2$ ,

$-NR^{2g} CONR^{2f} R^{2h}$ , wherein  $R^{2h}$  is selected from H,  $C_{1-6}$  alkyl,  $C_{1-4}$  haloalkyl,  $C_{1-4}$  alkoxy  $C_{1-4}$  alkyl,  $C_{3-6}$  cycloalkyl and  $C_{3-6}$  cycloalkyl $C_{1-6}$  alkyl;

30

$-NR^{2g} CO_2 R^{2e}$ ,

$-CONR^{2g} R^{2h}$ ,

1-morpholinyl,

168

1-piperidinyl,

1-piperazinyl,

and

C<sub>3-8</sub> cycloalkyl wherein 0-1 carbon atoms in the C<sub>4-8</sub>

5 cycloalkyl is replaced by a group selected from

-O-, -S(O)<sub>n</sub>-, -NR<sup>2g</sup>-, -NCO<sub>2</sub>R<sup>2e</sup>, -NCOR<sup>2e</sup>,and -NSO<sub>2</sub>R<sup>2e</sup>; and wherein N<sub>4</sub> in

1-piperazinyl is substituted with 0-1

substituents selected from R<sup>2g</sup>, CO<sub>2</sub>R<sup>2e</sup>, COR<sup>2e</sup> and10 SO<sub>2</sub>R<sup>2e</sup>; orthe group R<sup>2j</sup>, R<sup>2k</sup>, C<sub>1-6</sub> alkyl, C<sub>2-8</sub>alkenyl, C<sub>2-8</sub> alkynyl, Br, Cl, F, I, C<sub>1-4</sub> haloalkyl, -OR<sup>2g</sup>,-NR<sup>2g</sup>R<sup>2h</sup>, -C<sub>1-6</sub> alkylOR<sup>2g</sup>, and C<sub>3-8</sub> cycloalkyl which is15 substituted with 0-1 R<sup>2i</sup> and in which 0-1 carbons of C<sub>4-8</sub>  
cycloalkyl is replaced by -O-, whereinR<sup>2j</sup> is selected from heteroaryl wherein heteroaryl  
includes pyridyl, pyrimidinyl, triazinyl, furanyl,

20 quinolinyl, isoquinolinyl, thienyl, imidazolyl,

thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl,

benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl,

pyrazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-

dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, 2,3-

25 dihydrobenzothienyl-s-oxide, 2,3-dihydro-benzothienyl-S-

dioxide, indolinyl, benzoxazolin-2-onyl, benzodioxolanyl

and benzodioxane, each heteroaryl being substituted on 0-

4 carbon atoms with a substituent independently selected

from the group C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, Br, Cl, F, I, C<sub>1-4</sub>30 haloalkyl, -CN, nitro, OR<sup>2m</sup>, -SH, -S(O)<sub>n</sub>R<sup>2h</sup>, -COR<sup>2m</sup>, -OC(O)R<sup>2h</sup>, -NR<sup>2g</sup>COR<sup>2m</sup>, -N(COR<sup>2m</sup>)<sub>2</sub>, -NR<sup>2g</sup>CONR<sup>2o</sup>R<sup>2p</sup>, -NR<sup>2g</sup>CO<sub>2</sub>R<sup>2h</sup>, -NR<sup>2o</sup>R<sup>2p</sup> and -CONR<sup>2o</sup>R<sup>2p</sup> and each heteroaryl being substituted

on any nitrogen atom with 0-1 substituents selected from the group  $R^{2g}$ ,  $CO_2R^{2e}$ ,  $COR^{2e}$  and  $SO_2R^{2e}$ ;

$R^{2k}$  is heterocyclyl which is a saturated or partially saturated heteroaryl as defined for  $R^{2j}$ , each heterocyclyl being substituted on 0-4 carbon atoms with a substituent independently selected from the group  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl, Br, Cl, F, I,  $C_{1-4}$  haloalkyl, -CN, nitro,  $-OR^{2m}$ , -SH,  $-S(O)_nR^{2h}$ ,  $-COR^{2m}$ ,  $-OC(O)R^{2h}$ ,  $-NR^{2g}COR^{2m}$ ,  $-N(COR^{2m})_2$ ,  $-NR^{2g}CONR^{2o}R^{2p}$ ,  $NR^{2g}CO_2R^{2h}$ ,  $-NR^{2o}R^{2p}$  and  $-CONR^{2o}R^{2p}$  and each heterocyclyl being substituted on any nitrogen atom with 0-1 substituents selected from the group  $R^{2f}$ ,  $CO_2R^{2e}$ ,  $COR^{2e}$  and  $SO_2R^{2e}$ ;

wherein

$R^{2i}$  is H,  $C_{1-4}$  alkyl,  $C_{3-6}$  cycloalkyl- $C_{1-4}$  alkyl and  $C_{3-8}$  cycloalkyl;

$R^{2m}$  is H,  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl  $C_{1-6}$  alkyl,  $C_{1-2}$  alkyloxy  $C_{1-2}$  alkyl,  $C_{1-4}$  haloalkyl,  $R^{2g}S(O)_n-C_{1-4}$  alkyl and  $R^{2r}R^{2s}N-C_{2-4}$  alkyl;

$R^{2n}$  is H,  $C_{1-6}$  alkyl,  $C_{3-10}$  cycloalkyl,  $C_{3-6}$  cycloalkyl- $C_{1-6}$  alkyl,  $C_{1-2}$  alkyloxy  $C_{1-2}$  alkyl, and  $C_{1-4}$  haloalkyl;

$R^{2o}$  and  $R^{2p}$  are independently selected at each occurrence from H,  $C_{1-6}$  alkyl,  $C_{3-10}$  cycloalkyl,  $C_{3-6}$  cycloalkyl  $C_{1-6}$  alkyl and  $C_{1-4}$  haloalkyl;

$R^{2q}$  is selected from  $C_{1-6}$  alkyl,  $C_{1-4}$  haloalkyl,  $C_{1-4}$  alkoxy- $C_{1-4}$  alkyl,  $C_{3-6}$  cycloalkyl,  $C_{3-6}$  cycloalkyl- $C_{1-6}$  alkyl, aryl, aryl( $C_{1-4}$  alkyl), heteroaryl and heteroaryl ( $C_{1-4}$  alkyl)-

110

and benzyl, each benzyl being substituted on the aryl moiety with 0-1 substituents selected from the group  $C_{1-4}$  alkyl, Br, Cl, F, I,  $C_{1-4}$  haloalkyl, nitro,  $C_{1-4}$  alkoxy  $C_{1-4}$  haloalkoxy, and dimethylamino;

5

$R^{2r}R^{2s}$  taken together with the N form 1-pyrrolidinyl, 1-morpholinyl, 1-piperidinyl or 1-piperazinyl wherein  $N_4$  in 1-piperiazinyl is substituted with 0-1 substituents selected from the group  $R^{2t}$ ,  $CO_2R^{2q}$ ,  $COR^{2q}$  and  $SO_2R^{2q}$ ;

10

$R^{2t}$  is selected from H,  $C_{1-4}$  alkyl,  $C_{1-4}$  haloalkyl,  $C_{1-4}$  alkoxy  $-C_{1-4}$  alkyl,  $C_{3-6}$  cycloalkyl,  $C_{3-6}$  cycloalkyl  $-C_{1-6}$  alkyl, aryl, aryl ( $C_{1-4}$  alkyl)-, heteroaryl and heteroaryl ( $C_{1-4}$  alkyl);

15

$R^3$  is selected from an aryl or heteroaryl group attached through an unsaturated carbon atom;

aryl is selected from phenyl, naphthyl, indanyl and

20

indenyl, each aryl being substituted with 0-5 substituents independently selected at each occurrence from  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl, methylenedioxy,  $C_{1-4}$

alkyloxy- $C_{1-4}$  alkyloxy,  $-OR^{2m}$ , Br, Cl, F, I,  $C_{1-4}$  haloalkyl,  $-CN$ ,  $-NO_2$ ,  $-SH$ ,  $-S(O)_nR^{2n}$ ,  $-COR^{2m}$ ,  $-CO_2R^{2m}$ ,  $-OC(O)R^{2n}$ ,  $-$

25

$NR^{2q}COR^{2m}$ ,  $-N(COR^{2m})_2$ ,  $-NR^{2q}CONR^{2o}R^{2p}$ ,  $-NR^{2q}CO_2R^{2h}$ ,  $-NR^{2o}R^{2p}$  and  $CONR^{2o}R^{2p}$  and up to 1 phenyl, each phenyl substituent being substituted with 0-4 substituents selected from the group  $C_{1-3}$  alkyl,  $C_{1-3}$  alkoxy, Br, Cl, F, I,  $-CN$ , dimethylamino,  $CF_3$ ,  $C_2F_5$ ,  $OCF_3$ ,  $SO_2Me$  and acetyl;

30

heteroaryl is selected from the group pyridyl, pyrimidyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl,



## III

- benzofuranyl, benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzo-furanyl, 2,3-dihydrobenzothienyl, 2,3-dihydro-benzothienyl-S-oxide, 2,3-dihydrobenzothienyl-s-dioxide, indolinyl, benzoxazolin-2-on-yl, benzodioxolanyl and benzodioxane, each heteroaryl being substituted at 0-4 carbon atoms with a substituent independently selected at each occurrence from the group  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl, Br, F, I,  $C_{1-4}$  haloalkyl, -CN,  $NR^{2g}R^{2h}$ , nitro,  $-OR^{2m}$ , -SH, -S(O) $_nR^{2n}$ ,  $COR^{2m}$ ,  $-CO_2R^{2m}$ ,  $-OC(O)R^{2n}$ ,  $-NR^{2g}COR^{2m}$ ,  $-N(COR^{2m})_2$ ,  $-NR^{2g}CONR^{2o}R^{2p}$  and each heteroaryl being substituted at any nitrogen atom with 0-1 substituents selected from the group  $R^{2g}$ ,  $CO_2R^{3a}$ ,  $COR^{3a}$  and  $SO_2R^{3a}$  wherein,
- 15  $R^{3a}$  is selected from the group  $C_{1-6}$  alkyl,  $C_{1-4}$  cycloalkyl- $C_{1-6}$  alkyl and benzyl, each benzyl being substituted on the aryl moiety with 0-1 substituents selected from the group  $C_{1-4}$  alkyl, Br, Cl, F, I,  $C_{1-4}$  haloalkyl, nitro,  $C_{1-4}$  alkoxy,  $C_{1-4}$  haloalkoxy, and dimethylamino;
- 20  $R^4$  and  $R^5$  are independently selected at each occurrence from H, Br, Cl, F, I, -CN,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{3-8}$  cycloalkyl,  $C_{1-6}$  alkyloxy,  $C_{1-6}$  alkylthio,  $C_{1-6}$  alkylsulfinyl,  $C_{1-6}$  alkylsulfonyl, amino,  $C_{1-4}$  alkylamino, (C<sub>1-4</sub> alkyl)<sub>2</sub> amino and phenyl, each phenyl is substituted
- 25 with 0-3 groups selected from the group consisting of  $C_{1-7}$  alkyl,  $C_{3-8}$  cycloalkyl, Br, Cl, F, I, -C(O)H,  $C_{1-4}$  haloalkyl, nitro,  $C_{1-4}$  alkoxy,  $C_{1-4}$  haloalkoxy,  $C_{1-4}$  alkylthio,  $C_{1-4}$  alkylsulfinyl,  $C_{1-4}$  alkylsulfonyl,  $C_{1-6}$  alkylamino and (C<sub>1-4</sub> alkyl)<sub>2</sub> amino and wherein  $R^4$  and  $R^5$  non-phenyl groups may be substituted with 0-5
- 30 substituents selected from OH, halogen, -C(O)H,  $-OC_{1-6}$ -alkyl and  $C_{1-6}$  haloalkyl,  $C_{1-6}$  alkyl,  $C_{3-7}$  c-alkyl,  $C_{1-6}$

112

alkyl(OH)<sub>n</sub>CO<sub>2</sub>R wherein R is H or C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkyl(OH)<sub>n</sub>, wherein n is 0-3 or R<sup>4</sup> and R<sup>5</sup> may join together to form a C<sub>3-6</sub> alkylene chain.

5

3. The compound according to Claim 1 or 2 wherein

R<sup>1</sup> is selected from C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkylthio, -XR<sup>1c</sup> wherein R<sup>1</sup> is substituted with  
10 0-6 substituents selected from halogen, C<sub>1-4</sub> alkyl or C<sub>1-4</sub> haloalkyl;

R<sup>2</sup> is selected from substituted-C<sub>1-10</sub> alkyl, branched C<sub>3-10</sub> alkyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-8</sub> cycloalkyl, C<sub>3-6</sub> cycloalkyl C<sub>1-6</sub> alkyl, -NR<sup>2c</sup>R<sup>2d</sup> wherein, in the case of  
15 substituted-C<sub>1-10</sub> alkyl, 1-3 substituents are independently selected from the group R<sup>2i</sup>, R<sup>2j</sup>, R<sup>2k</sup>, C<sub>1-6</sub> alkyl, C<sub>2-8</sub> alkenyl, C<sub>2-8</sub> alkynyl, Br, Cl, F, I, C<sub>1-4</sub> haloalkyl, -OR<sup>2g</sup>, -NR<sup>2g</sup>R<sup>2h</sup>, -C<sub>1-6</sub> alkylOR<sup>2g</sup>, and C<sub>3-8</sub> cycloalkyl  
20 which is substituted with 0-1 R<sup>2i</sup> and in which 0-1 carbons of C<sub>4-8</sub> cycloalkyl is replaced by -O- and wherein the R<sup>2</sup> groups, other than substituted-C<sub>1-10</sub> alkyl, are substituted with 0-3 substituents independently selected from the group R<sup>2i</sup>, R<sup>2j</sup>, R<sup>2k</sup>, C<sub>1-6</sub> alkyl, C<sub>2-8</sub> alkenyl, C<sub>2-8</sub> alkynyl, Br,  
25 Cl, F, I, C<sub>1-4</sub> haloalkyl, -OR<sup>2g</sup>, -NR<sup>2g</sup>R<sup>2h</sup>, -C<sub>1-6</sub> alkylOR<sup>2g</sup>, and C<sub>3-8</sub> cycloalkyl which is substituted with 0-1 R<sup>2i</sup> and in which 0-1 carbons of C<sub>4-8</sub> cycloalkyl is replaced by -O-.

4. The compound according to Claims 1 or 2 or 3 wherein  
30 R<sup>3</sup> is selected from an aryl group selected from phenyl or substituted versions thereof or a heteroaryl group selected from pyridyl or substituted versions thereof.

113

5. The compound according to Claims 1,2,3 or 4 wherein  $R^2$  is selected from  $C_1$  alkyl of the formula  $-CR'R''$  wherein  $R'$ ,  $R''$  and  $R'''$  are independently selected from H,  $C_{1-6}$  alkyl,  $C_{3-7}$  cycloalkyl, hydroxy $C_{1-6}$  alkyl,  $C_{1-6}$  alkyloxy $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{1-6}$  alkyloxy, hydroxy, with the proviso that each of  $R'$ ,  $R''$  and  $R'''$  cannot be H;

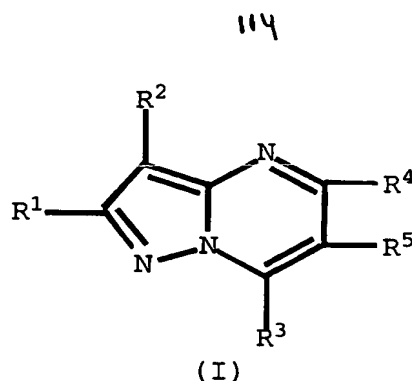
or  $R^2$  is selected from  $NR^{2c}R^{2d}$  wherein  $R^{2c}$  and  $R^{2d}$  are independently selected from H or  $C_{1-6}$  alkyl.

10

6. The compound according to Claims 1-5 wherein  $R^3$  is selected from an aryl or heteroaryl group attached through an unsaturated carbon atom wherein, aryl is phenyl, each phenyl being substituted with 0-5 substituents independently selected at each occurrence from  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl, methylenedioxy,  $C_{1-4}$  alkyloxy- $C_{1-4}$  alkyloxy,  $-OR^{2m}$ , Br, Cl, F, I,  $C_{1-4}$  haloalkyl,  $-CN$ ,  $-NO_2$ ,  $-SH$ ,  $-S(O)_nR^{2n}$ ,  $-COR^{2m}$ ,  $-CO_2R^{2m}$ ,  $-OC(O)R^{2n}$ ,  $-NR^{2q}COR^{2m}$ ,  $-N(COR^{2m})_2$ ,  $-NR^{2q}CONR^{2o}R^{2p}$ ,  $-NR^{2q}CO_2R^{2h}$ ,  $-NR^{2o}R^{2p}$  and  $CONR^{2o}R^{2p}$  and up to 1 phenyl, each phenyl substituent being substituted with 0-4 substituents selected from the group  $C_{1-3}$  alkyl,  $C_{1-3}$  alkoxy, Br, Cl, F, I,  $-CN$ , dimethylamino,  $CF_3$ ,  $C_2F_5$ ,  $OCF_3$ ,  $SO_2Me$  and acetyl and wherein, heteroaryl is selected at each occurrence from pyridyl, each pyridyl being substituted at 0-4 carbon atoms with a substituent independently selected at each occurrence from the group  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl, Br, F, I,  $C_{1-4}$  haloalkyl,  $-CN$ , nitro,  $-OR^{2m}$ ,  $-SH$ ,  $-S(O)_nR^{2n}$ ,  $COR^{2m}$ ,  $-CO_2R^{2m}$ ,  $-OC(O)R^{2n}$ ,  $-NR^{2q}COR^{2m}$ ,  $-N(COR^{2m})_2$ ,  $-NR^{2q}CONR^{2o}R^{2p}$  and each pyridyl being substituted at any nitrogen atom with 0-1 substituents selected from the group  $R^{2q}$ ,  $CO_2R^{3a}$ ,  $COR^{3a}$  and  $SO_2R^{3a}$ .

20

7. A compound of formula (I)



or a pharmaceutically acceptable salt, stereoisomer or prodrug thereof, wherein

5

$R^1$  is selected from  $C_{1-6}$  alkyl,  $C_{1-6}$  alkyloxy, -SH or OH;

$R^2$  is selected from  $C_{1-4}$  alkyl which is unsubstituted or substituted with 1-4 substituents selected from  $C_{1-6}$  alkyl,  $C_{3-8}$  cycloalkyl,  $C_{1-6}$  alkylOR<sup>2g</sup>,  $C_{2-6}$  alkenyl or OR<sup>2g</sup> wherein  $R^{2g}$  is H or  $C_{1-6}$  alkyl;

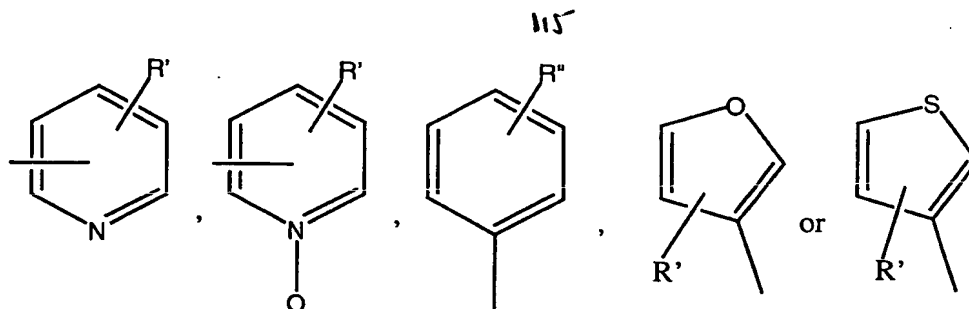
10

$R^3$  is selected from an aryl or heteroaryl group bonded through an unsaturated carbon atom that is unsubstituted or substituted with 1-4 substituents selected from Cl, F, I, Br, -OH, CF<sub>3</sub>, S(O)<sub>n</sub>C<sub>1-6</sub> alkyl, -OC<sub>1-6</sub> alkyl,  $C_{1-6}$  alkyl or NR<sup>2g</sup>R<sup>2h</sup> wherein  $R^{2g}$  and  $R^{2h}$  are independently selected from H or  $C_{1-6}$  alkyl;

15

$R^4$  and  $R^5$  are independently selected from H,  $C_{1-6}$  alkyl or  $C_{1-6}$  alkyloxy, with the proviso that when  $R^1$  and  $R^2$  are unsubstituted, unbranched  $C_{1-3}$  alkyl,  $R^3$  may not be

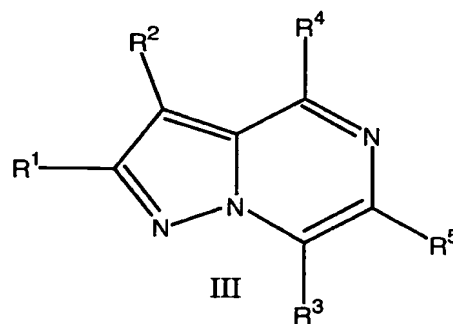
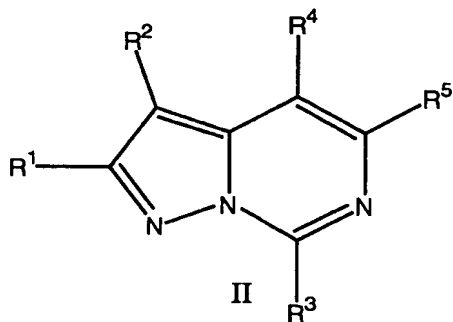
20



wherein R' is H or C<sub>1-3</sub> alkyl and R'' is H or o-trifluoromethyl, m-trifluoromethyl or m-methoxy.

8. The compound according to Claims 1-7 wherein R' is substituted with 2-4 substituents.

9. A compound of the formula:



or a pharmaceutically acceptable salt or isomer thereof wherein R<sup>1</sup>-R<sup>5</sup> and other variables are as defined in claims 1-8.

10. Use of a compound according to Claims 1-9 in therapy.

11. Use of a compound according to Claims 1-9 to antagonize a CRF-1 receptor in mammals including humans wherein binding to the receptor causes and ultimately

results in the treatment of affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of according to Claims 1-9.

12. A pharmaceutical composition comprising a compound according to Claims 1-9 and a pharmaceutically acceptable carrier with the proviso that, in a compound of formula I according to Claim 1, proviso (d) compounds are not excluded.